Confidential

Expert Report of Steven P. Cohen, M.D.

MDL No. 2804

Relating to Case Nos. 17-OP-45004 and 18-OP-45090

Table of Contents

I. PURPOSE

I was retained by Johnson & Johnson and Janssen Pharmaceuticals, Inc. for the purposes of rendering an expert opinion in this matter. The purpose of this report is to provide a brief tutorial on the nature of pain and its modern management in the United States. Within this topic, I have been asked to opine on the role of prescription opioid medications for treating pain, with a particular focus on chronic non-cancer pain. This report: (1) outlines the rationale for the use of opioids in general, and Duragesic, Nucynta, and Nucynta ER in particular; (2) provides an overview of the risks and benefits of opioid prescribing, along with clinical aspects of chronic pain treatment; and (3) discusses the practices and state of medical knowledge regarding the use of prescription opioid medications. The report also addresses the opinions of certain plaintiffs' experts, including Drs. David Kessler, Anna Lembke, and Mark Schumacher, as well as the testimony of Cuyahoga County witness Dr. Thomas Gilson.

I am offering the opinions below to a reasonable degree of medical and scientific certainty. My opinions are based on my education, training, clinical experience, skill, knowledge, and research, as well as on my analysis of relevant records, publications, and reports. I reserve the right to testify in my areas of expertise in response to the testimony of the plaintiffs' experts. I also reserve the right to supplement and revise my opinions based on new information.

II. MY BACKGROUND & QUALIFICATIONS

I am an anesthesiologist and interventional pain management specialist and have been continuously licensed as a physician since 1991, having previous licenses in New York, Pennsylvania and Massachusetts. I currently work and have a license to practice medicine in Maryland. I obtained my medical degree from the Mount Sinai School of Medicine, completed an internal medicine internship at the Beth Israel Medical Center in New York, a residency in anesthesiology at Columbia University, and a pain medicine fellowship at the Massachusetts General Hospital, Harvard Medical School. I am board certified by the American Board of Anesthesiology with added qualifications in Pain Management.

I am currently the Chief of Pain Medicine, and Director of the Blaustein Pain Treatment Center, at Johns Hopkins School of Medicine, where I also hold joint faculty appointments as a Professor of Anesthesiology & Critical Care Medicine, Neurology, and Physical Medicine & Rehabilitation. I hold additional appointments as a Professor of Anesthesiology and Physical Medicine & Rehabilitation at the Uniformed Services University of the Health Sciences, and from 2005 through 2019 served as Director of Pain Research at Walter Reed National Military Medical Center. Among others, I am or have been a member of the American Academy of Pain Medicine (AAPM), the American Society of Regional Anesthesia and Pain Medicine (ASRA), the American Pain Society, the American Society of Anesthesiologists, the American Society of Interventional Pain Physicians, and the Spinal Intervention Society. I currently serve on the Boards of Directors for AAPM and ASRA and have previously been Chair of both annual conferences.

I am a retired Colonel in the U.S. Army. During my time as active military, I was deployed four times (1995 to 1996, 2003, 2004 to 2005, and 2007 to 2008) in support of operations in Bosnia, Iraq and Afghanistan. I also served as the Reserve Liaison to the Pain Management Consultants to the U.S. Army and Navy Surgeons General. From 2002 to 2007 I was Chief of Anesthesia & Operative Services at the 4219th Combat Support Hospital in Picatinny Arsenal, New Jersey. From 2007 to 2008 I served as Deputy Commander for the Clinical Services for the 48th Combat Support Hospital at Fort George Meade, Maryland, which is equivalent to the Chief Medical Officer for the unit. I served as Chief of Anesthesia & Operative Services at the 48th Combat Support Hospital from 2007 to 2014. I have presented data on pain management in service members to the U.S. Congress, FDA and General Officers. I conducted research that was involved in the passage of the 2008 Military Pain Care Act, and served as an inaugural member of the U.S. Army Medical Advisory Board.

I have over 300 peer-reviewed publications and book chapters on pain in such journals as Lancet, BMJ, Annals of Internal Medicine, JAMA Internal Medicine, New England Journal of Medicine, Anesthesiology and Pain and have been the First Author on the past 3 editions of the 'Pain' chapter for Cecil Textbook of Medicine. Among my contributions to the field of pain medicine are the development of an FDA-approved denervation technique for treating sacroiliac joint pain, helping set up the first pain clinic in a war zone, performing the first studies evaluating the epidural administration of biological agents for pain, serving as the Senior Investigator on the Congressionally-mandated study evaluating compounded topical creams for chronic pain (2014 National Defense Authorization Act, HR 33014), serving as Committee Chair for the ASRA/ AAPM/ ASA ketamine guidelines for pain management, serving as Committee Chair for an international consortium developing guidelines for the treatment of low back pain arthritis with blocks and radiofrequency ablation, and conducting research on facet arthropathy and epidural steroid injections that has changed the way the conditions is viewed and treated. I was the lead speaker at the 2014 panel the FDA convened on the effectiveness and safety of epidural steroid injections. I have also been consulted by several other similar regulatory agencies in other countries to discuss back pain, including the UK's National Health Service in 2019.

A copy of my curriculum vitae more fully setting forth my experience and professional accomplishments is attached as Exhibit A.

III. FOUNDATIONS OF PAIN MEDICINE

A. BRIEF HISTORY OF PAIN AND ITS TREATMENT

Evidence that man has been afflicted with pain since his beginning is incontrovertible. References to pain transcend all races and cultures. Pain is also a vital diagnostic clue for physicians, being the most common symptom for which patients seek medical attention.

Pain medicine began as a specialty in recognition of the scope of the problem, and realization that poorly treated pain can have adverse, long-term biological, psychological and social consequences that are highly variable from individual to individual (i.e. biopsychosocial

model; *Engel G. Science 1977; Fillingim et al. Pain 2017*). Studies were published demonstrating the high prevalence rates of chronic pain and its undertreatment, particularly in vulnerable populations such as the elderly and children (*Howard RF. JAMA 2003; Neighbor et al. Acad Emerg Med 2004; Sittl et al. Schmerz 2000; Dalacorte et al. N Am J Med Sci 2011*). In 1946, following service in WWII, John Bonica established the first multidisciplinary pain clinic at the University of Washington, and in 1953 published the historic textbook 'Management of Pain'. Later in 1973, he would go on to found the International Association for the Study of Pain, which was followed by subsidiary chapters all of the world including the American Pain Society, which was formed in 1977. Another major breakthrough occurred in 1965, when Melzack and Wall published their landmark article on the gate control theory (*Melzack and Wall. Science 1965*).

B. CLASSIFICATION OF PAIN STATES

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage" (*IASP Terminology, https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698*). This definition recognizes that pain may occur in the absence of ongoing tissue damage, such as fibromyalgia or phantom limb pain. One implication of this construct is the assumption that pain is subjective; hence a patient's report of pain should be accepted at face value in the absence of evidence to the contrary, although physicians have developed ways to confirm patient reports (e.g. facial expressions, vital signs for acute pain, advanced imaging, historical and physical exam findings such as Waddell signs).

1. ACUTE VS. CHRONIC PAIN

Multiple classifications have been used to describe pain states based on duration, anatomical source, and mechanisms. Acute pain results from injury or inflammation, has survival value, and may play a role in healing by promoting behaviors that minimize re-injury. For generations, opioids have been the mainstay for acute pain management (*Power I. Br J Anaesth 2011; Macintyre et al. Anaesth Intensive Care 2011*). Although there is no clear threshold where acute pain transitions to a chronic state, it is generally accepted that pain which persists beyond the expected healing period is pathological. In most cases, this period is between 3 and 6 months. The intensity of pain can be classified by intensity as mild (1-3), moderate (4-7) or severe (> 7 on a 0-10 scale).

In patients with persistent pain, several terms have been used to describe patterns. Baseline pain is that which is almost always present and may be described as continuous, steady, or constant. It can be partly or completely masked if controlled by effective analgesic management, usually by long-acting or sustained-release opioids (*Fine et al. Pain Med 2009; Vallerand AH. Nurs Clin North Am 2003*).

Breakthrough pain is a transitory exacerbation of pain experienced by a patient who has relatively stable and adequately controlled baseline pain, usually from opioids (*Portenoy and Hagen. Pain 1990*). First described by Portenoy and Hagen in 1989 (*Portenoy and Hagen.*

Oncology 1989), this definition has been accepted and utilized used by numerous organizations, including the European Association for Palliative Care (*Mercadente et al. Consensus Conference on an Expert Working Group of the European Association for Palliative Care, setting forth knowledge on BTP. Cancer 2002*). The term breakthrough pain can refer to an exacerbation of the baseline pain or represent pain with a different cause from that of the baseline pain. Unlike baseline pain, breakthrough pain is often spontaneous and unpredictable.

Incident pain is breakthrough pain that occurs as a predictable or unpredictable response to an individual's actions (e.g. activity). End-of-dose failure refers to pain that arises when a long-acting medication, generally an opioid, wears off and the blood levels fall below the therapeutic analgesic threshold. In patients with near-constant pain on long-acting opioids, one way to treat end-of-dose failure is to change the dosing frequency (i.e. changing q12 hour Oxycontin to every 8 hours, or changing Duragesic from q72 hours to every 48 hours).

2. SOMATIC AND VISCERAL PAIN

Pain can originate from somatic or visceral structures. Somatic pain is typically well-localized and results from injury or disease of the skin and musculoskeletal structures. Different types of stimulation can evoke pain by binding to distinct receptors (a.k.a. nociceptors), which are categorized as either polymodal (which respond to painful and non-painful stimuli) or nociceptive specific, which respond to mechanical, temperature or chemical stimuli. Visceral pain arises from internal organ dysfunction, and can result from inflammation, ischemia, occlusion of flow (e.g. renal stones, bowel obstruction), or functional pathology (e.g. irritable bowel syndrome). In contrast to somatic pain, visceral pain is usually diffuse and poorly localized, is often referred to somatic regions (e.g. myocardial ischemia radiating into the arm), and tends to be associated with exaggerated autonomic reflexes and greater emotional features. Reasons for these differences include a lower density and different types of nociceptors, and convergence with afferent pathways in the spinal cord.

3. NEUROPATHIC, NOCICEPTIVE, NOCIPLASTIC AND MIXED PAIN

Pain can be etiologically classified as neuropathic, nociceptive, or mixed. This distinction is perhaps the most useful, as it affects decision making at all levels of care. Neuropathic pain is defined as pain caused by a lesion or disease affecting the somatosensory system. Common peripheral neuropathic pain states include diabetic neuropathy and radicular pain. One subtype of neuropathic is central pain, which manifests as a constellation of symptoms following a lesion affecting the central nervous system. Owing to its high prevalence, the most common overall cause of central pain is central post-stroke pain (occurring after approximately 8% of cerebrovascular accidents), though spinal cord lesions are associated with a higher incidence of central pain (> 50%). Nociceptive pain results from an injury or disease affecting somatic structures such as skin, muscle, tendons, bone and joints. Nocicplastic pain, codified by the International Association for the Study of Pain in 2017, is pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors, or evidence for disease or lesion of the somatosensory

system causing the pain. Formerly known as "functional pain syndromes", these conditions include pain states such as fibromyalgia, irritable bowel syndrome and possibly even non-specific back pain. The precise pathophysiological mechanisms responsible for these disorders are still being elucidated, though they likely include augmented sensory processing, diminished inhibitory pathways, and a higher co-prevalence rate of conditions associated with chronic pain such as mood and sleep disorders. Mixed pain is pain that contains significant portions of both neuropathic and nociceptive pain. Pain associated with cancer can result from either the tumor itself or as a consequence of therapy (e.g., surgery, chemo- and radiation therapy), and advanced malignancies typically include neuropathic, nociceptive and nociplastic components. Other examples of mixed pain conditions include failed back surgery syndrome, radiculopathy, headache and ischemic pain.

IV. BURDEN OF CHRONIC PAIN

A. CHRONIC PAIN IS A SIGNIFICANT PROBLEM IN THE UNITED STATES REQUIRING TREATMENT

It is difficult to overestimate the impact pain holds on society. According to the 2012 National Health Interview Study involving 8781 respondents, 55.7% of adults reported pain in previous 3 months, with 10.3% suffering from daily pain and 11.2% having severe pain (*Nahin et al. J Pain 2015*). The undertreatment of chronic pain was recognized back in the 1980's, as evidenced by a 1987 New York Times article citing a survey that found that 65% of hospital patients in pain were undertreated, and a 1982 editorial in the New England Journal of Medicine entitled 'The Quality of Mercy' (*Goleman D. Physicians Said to Persist in Undertreating Pain and Ignoring the Evidence. NY Times, Dec 31, 1987; Angell M. N Engl J Med 1982; Donovan et al. Pain 1987*). Among the various causes of worldwide disability, four (back pain, neck pain, headaches and musculoskeletal conditions such as arthritis) of the top ten are pain conditions (*GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Lancet 2018*). Populations at high risk for chronic pain include the elderly, and individuals with physical and psychological morbidities. Based on estimates from the 2008 Medical Expenditure Panel Survey examining the economic burden of pain in the United States, co-sponsored by the Agency for Healthcare Research and Quality and the National Center for Health Statistics, the annual cost of pain were estimated as ranging between $560 and $635 billion in 2010 U.S. dollars (*Gaskin & Richard. J Pain 2012*).

In the U.S., rates of chronic pain prevalence vary from 11% to 40%, with a recent Centers for Disease Control and Prevention study estimating it at 20.4% in 2016 (*Dahlhamer et al. MMWR Sept. 14, 2018; Pitcher et al. J Pain 2019*). In another highly cited study, Nahin estimated that 55.7% of U.S. adults experienced pain in the past 3 months, with 32% experiencing pain every or almost every day, and 11.2% reporting severe, debilitating pain (*Nahin RL. J Pain 2015*). Among the 4 leading causes of years lost to disability, 3 are chronic pain conditions: low back pain (LBP), which represents the leading cause of disability; musculoskeletal disorders which ranks 3rd; and neck pain, which comes in at number 4 (*US Burden of Disease Collaborators. JAMA 2013; 310: 591-608*). A report released in 2010, the

Institute of Medicine estimated that chronic pain afflicts 1 out of 3 Americans, costing between $560 and $635 billion (in 2010 dollars) per year in medical costs and lost productivity. Moreover, the prevalence of chronic pain appears to be increasing for several reasons including the aging of the population, rising rates of obesity, increased survival rates after trauma, a higher proportion of surgical procedures being done on an outpatient basis (which can lead to under-treatment), and improved surveillance and reporting (*Institute of Medicine Report from the Committee on Advancing Pain Research, Care, and Education: Relieving Pain in America, A Blueprint for Transforming Prevention, Care, Education and Research. The National Academies Press, 2011. Available at: http://books.nap.edu/openbook.php?record_id=13172*). For these reasons, it is my opinion that the lack of proper treatment for chronic pain patients poses a serious public health problem (*Raffaeli and Arnaudo. J Pain Res 2017; Kroenke and Cheville JAMA 2017*).

B. SPECIFIC POPULATIONS AT HIGH RISK FOR CHRONIC PAIN

Pain can disproportionately affect particular individuals and communities, and some parts of the United States are more affected than others. Studies have found that African Americans have higher pain prevalence rates for conditions such as headache, arthritis and other musculoskeletal conditions than other racial groups (*Edwards et al. Psychosom Med 2001*), and that pain tends to be undertreated in African Americans and Latinos (*Tamayo-Sarver et al. Am J Public Health 2003; Bernabei et al. JAMA 1998; Green et al. Pain Med 2003*). Native Americans report dramatically higher rates of certain types of chronic pain than other ethnic groups (*CDC and NCHS (National Center for Health Statistics). Health, United States, 2010. Hyattsville, MD: CDC and NCHS; 2010. Chart-book, Special feature on death and dying*).

Compared to individuals with higher levels of education and income, individuals living in poverty having higher pain prevalence rates for many conditions, and have less access to treatment (*Portenoy et al. J Pain 2004; CDC and NCHS (National Center for Health Statistics). Health, United States, 2010*). Females are more likely to report and experience pain than males across geographical regions and racial categories (*Fillingim et al. J Pain 2009*). In children, pain has been shown to be under-recognized and undertreated (*Winner P. Curr Treat Options Neurol 2004; Alexander and Manno. Ann Emerg Med 2003*). Whereas aging is associated with a decline in pain sensitivity (*Lin et al. J Peripher Nerv Syst 2005*), the elderly experience increased chronic pain prevalence and are often under-treated with analgesics (*Murphy et al. Am J Ther 2018; Bernabei et al. JAMA 1998*). Several other factors may affect the prevalence of chronic pain and/ or decreased access to care, including living in a rural area, being in the military, cognitive impairment and being at the end of life (*CDC and NCHS (National Center for Health Statistics). Health, United States, 2010; Cohen et al. Spine J 2012; Jones et al. Vital Health Stat 13 2009; Ferrell et al. J Pain Symptom Manage 1995; Paice JA. Pain at the end of life. In: Ferrell BR, Coyle N, editors. Oxford textbook of palliative nursing. 3rd ed. New York: Oxford University Press, Inc; 2010*).

C. SOURCES OF CHRONIC PAIN

There are many different types of chronic pain, with the most common being headache (45% with active diagnosis, > 70% with lifetime diagnosis; *Stovner et al. Cephalalgia 2007; Jensen and Stovner. Lancet Neurol 2008*), low back pain (mean annual prevalence 38%, *Hoy et al. Best Pract Res Clin Rheumatol 2010*), and neck pain (lifetime prevalence 48%, *Fejer et al. Eur Spine J 2006*). Among years lost to disability, low back and neck pain rank 1st, migraine 7th, osteoarthritis 13th, and other musculoskeletal disorders 8th (*GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Lancet 2016*).

Table 1. Classification & Prevalence of Common Pain Condit ions

Neuropathic		Nociceptive		Nociplastic	Mixed
Peripheral	**Central**	**Somatic**	**Visceral**		
Peripheral neuropathy (1-3%)	Central post-stroke pain (8%)	Arthritis (25-40% in people > 40 years)	Endometriosis (10% in women of reproductive age)	Irritable bowel syndrome (5-15%)	Headache (15% for migraine, 20-30% for tension-type)
Postherpetic neuralgia (annual incidence 0.1-0.2%)	Spinal cord injury (30-50%)	Myofascial pain (5%-10%)	Interstitial cystitis (0.2-1% of women)	Fibromyalgia (3-6%)	Cancer (lifetime prevalence 30-40%)
Chronic postsurgical pain (2-10% after surgery)	Multiple sclerosis (25%)	Connective tissue disorders (0.2-0.5%)	Ulcers/ gastritis/ esophagitis (3-9%)	Complex regional pain syndrome type I (0.006-0.05%, 3%-20% after orthopedic surgery)	Low back pain (annual prevalence rate *20*-40%)
Phantom limb pain (30-60%)	Parkinson's disease (10%)	Burn pain (annual incidence of burns requiring hospitalization 0.01%)	Cholecystitis/ appendicitis	Temporomandibular disorder (5-12%)	Neck pain (annual prevalence rate *20*-40%)
Trigeminal neuralgia (0.01%)	Seizure disorder (1-3%)				Ischemic pain
Radiculopathy/ spinal stenosis (3%-10%)					
Nerve entrapment syndromes (e.g. carpal tunnel, thoracic outlet, meralgia paresthetica; 2-4%)					

Source: Cohen and Raja. Pain. Cecil Textbook of Medicine 2019.

D. CHRONIC PAIN AS A DISEASE MODEL

Pain is an integral part of life, an evolutionary critical warning system of danger to the organism. However, once the acute period of danger (i.e. bee sting, twisted ankle, burn) is over,

pain no longer becomes an evolutionary necessary, but a burden—a disease unto itself (*Treede et al. Pain 2019; Raffaeli and Arnaudo. J Pain Res 2017; Coluzzi et al. 2017; Greenberg EN. Journal of Pain & Palliative Care Pharmacotherapy 2012*). Chronic pain can lead to depression and anxiety, sleep disturbances, marital difficulties and other social problems, vocational and avocational disability, and deleterious changes in the nervous system that predispose individuals to other chronic pain conditions (*Woolf CJ. Nature 1983; Cohen and Raja. Pain. Cecil Textbook of Medicine 2019; Turk et al. IMMPACT recommendations. Pain 2003*). There is some evidence that the effective treatment of pain may reverse some of these changes (*Seminowicz et al. J Neurosci 2011; Cohen et al. Reg Anesth Pain Med 2018*). For example, in a double-blind, placebo-controlled study in amputees, Huse et al. found that opioids were not only efficacious in treatment, but also reversed cortical reorganization in the central nervous system (*Huse et al. Pain 2001*).

V. TREATING CHRONIC PAIN IS HIGHLY & INHERENTLY INDIVIDUALIZED

A. DOSE VARIATION

Doses of medications vary dramatically for the treatment of chronic pain. For example, a recent review for duloxetine, a treatment for neuropathic pain that is approved for musculoskeletal pain and fibromyalgia as well, found widely varying response rates (*Moore et al. Eur J Pain 2014*). Similar results have been shown for gabapentin and NSAIDs (*Yang et al. Korean J Anesthesiol 2013; Backonja and Glanzman. Clin Ther 2003; Pergolizzi et al. Pain Manag 2016*). For opioids, the dose required to obtain benefit even for acute pain varies dramatically (*Somogyi et al. Clin Pharmacol 2007*), and there is a large variation in the response to chronic pain, including for transdermal fentanyl (*Nugent et al. J Pain Symptom Manage 2001; Simmonds and Richenbacher. J Pain Symptom Manage 1992*). Wide variations in response rates have also been shown for procedures such as epidural steroid injections and radiofrequency ablation (*Cohen et al. Reg Anesth Pain Med 2013; Cohen et al. Nat Rev Rheumatol 2013*).

Using Higher Doses Than Those Recommended by the CDC Guidelines

In 2016, the CDC issued a guideline regarding the use of opioids to treat chronic non-cancer pain (*Dowell et al. MMWR (Mar. 18, 2016) and Errata (Mar. 26, 2016)*). The guidelines espoused by the CDC are only guidelines. Unlike standards, guidelines come with lower authority, and are designed to be more flexible; they do not constitute 'standard of care' and are only one aspect of an individualized, patient-oriented approach. In its 2013 response to the citizen's petition submitted by Physicians for Responsible Opioid Prescribing (PROP), Docket No. FDA-2012-P-0818, the FDA noted that although "available data do suggest a relationship between increasing opioid dose and risk of certain adverse effects... the available information does not demonstrate that the relationship is necessarily a causal one". During the November 2018 meeting of the American Medical Association House of Delegates, the organization confirmed that "some patients with acute or chronic pain can benefit from taking opioid pain medications at doses greater than generally recommended in the CDC Guidelines for Prescribing Opioids for Chronic Pain, and that such care may be medically necessary". They further asserted

that the "thresholds in the document should be considered guidance". Even some of the authors of the CDC guidelines acknowledge that some policies and practices that some entities have adopted following the guidelines have been inconsistent with, and go beyond, the CDC's recommendations (*Dowell et al. N Engl J Med 2019*). These inconsistences were highlighted in a recent consensus panel report, which highlighted inflexible application of the recommended dose and duration thresholds, policies that encourage and enforce 'hard' limits, and abrupt tapering of dosages (*Kroenke et al. Pain Med 2019*).

It is important to note that guidelines by numerous other countries including those in Latin America (*Lara-Solares et al. Latin-American guidelines for opioid use in chronic nononcologic pain. Pain Manage 2017, 200 morphine equivalents per day*), Japan (*The Committee for the Guidelines for Prescribing Opioid Analgesics for Chronic Non-cancer Pain of JSPC. Guidelines for prescribing opioid analgesics for chronic non-cancer pain. Tokyo, Shinko Trading Press. 2012, 120 morphine equivalents per day*), and Korea (*Kim ED et al. Korean J Pain 2017; mentions that "dose control" should be performed at 90 morphine equivalents per day, and that most cases of non-cancer pain should be controlled at doses not exceeding 180 morphine equivalents per day*) have designated higher cutoffs than those mentioned in the CDC guidelines.

B. VARIABILITY IN PAIN EXPERIENCE AND TOLERANCE

Everyone experiences pain differently. Pain is different from nociception (which is what is tested in animal models and contributes to the high failure in translation from bench to bedside analgesics) in that it involves not only the pathophysiological response to nerve or tissue injury, but contains elements that include affective components (e.g. anxiety, depression, fear), cognitive functions (beliefs, past experiences and memories), and context (e.g. cultural expectations, context). For example, the same painful stimulus experienced when a person is alone at night, without distractions, is likely to be perceived differently than when it occurs during a sporting event (*Lumley et al. J Clin Psychol 2011*). Not only is there inter-individual variability in pain perception, but there is also intra-variability such that pain may be experienced differently by the same individual at different points in their life (i.e. when someone is depressed or anxious, they are more likely to develop chronic pain after an acute pain episode than when things are going well) (*Kehlet et al. Lancet 2006; Berube et al. Int J Orthop Trauma Nurs 2017*). For this reason, pain is often described as having both sensory-discriminative and affective-motivational components (*Cohen and Mao. BMJ 2014*). Studies have generally shown a poor correlation between objective pathology and pain perception for conditions such as back pain, spinal stenosis and osteoarthritis (*Burgstaller et al. Spine (Phila PA 1976) 2016; Weber et al. (Phila PA 1976) 2016; Ai F et al. J Huazhong Univ Sci Technolog Med Sci 2010; Hansen et al. Best Pract Res Clin Rheumatol. 2016*).

There are many factors that affect pain perception (i.e. thresholds for feeling pain) and tolerance. These include genetics, age, sex, psychological factors, culture, expectations, context, co-morbidities, prior and current pain experiences, concomitant medications and other factors (*Bueno-Gómez N. Philos Ethics Humanit Med 2017; Wood S. Nurs Times 2010; Crofford LJ.*

Trans Am Clin Climatol Assoc 2015). The inability to fully delineate these factors, which are dynamic, may explain the wide range in therapeutic responses to pain interventions.

C. CHRONIC PAIN PATIENTS HAVE DIVERSE NEEDS THAT PHYSICIANS MUST TAKE INTO ACCOUNT WHEN DECIDING ON TREATMENT

Patients have different needs, based on their lifestyle and responsibilities, belief, culture, financial constraints, etc. These can be observed by the push to incorporate patient preferences into evidence-based medicine and clinical practice guidelines (*van der Weidjen et al. Implement Sci 2010; Siminoff LA. BMC Med Inform Decis Mak 2013*). For some patients with chronic pain, 'prescribing' a 6-month exercise program will not work, as pain may limit their ability to engage in physical activities, and their pain levels may adversely affect motivation. Some patients may not be candidates for opioid therapy, but some who have failed other treatments, or cannot receive them because of health reasons, may be excellent candidates for opioids. The NIH, along with multiple other research organizations, have recently launched a program attempting to understand how a person's individual genetics, environment and lifestyle can be used to guide treatment, called the 'Precision Medicine Initiative' (available at: *https://ghr.nlm.nih.gov/primer/precisionmedicine/initiative*). This approach has been advocated for chronic opioid therapy in order to optimize outcomes and minimize risks, though the authors acknowledge that more data is needed before widespread implementation (*Bruehl et al. J Pain 2013*).

VI. NON-OPIOID TREATMENTS FOR CHRONIC PAIN HAVE SIGNIFICANT LIMITATIONS

Any one treatment modality for chronic pain affords significant relief to only a small minority of patients, such that the placebo effect exceeds the intrinsic effect of nearly every pharmacological and interventional treatment across large populations. For neuropathic pain, first-line adjuvants such as antidepressants and gabapentinoids provide meaningful relief greater than placebo in less than one-third of patients (*Finnerup et al. MedGenMed 2007; Finnerup et al. Lancet Neurol 2015; Swedish Council on Health Technology Assessment, 2006*). For non-neuropathic pain, non-steroidal anti-inflammatory drugs alleviate pain in between 1 in 3 and 1 in 9 patients based on randomized trials, and acetaminophen has been shown to be ineffective for back pain and osteoarthritis (*Moore et al. Pain Pract 2014; Saragiotto et al. Cochrane Database Syst Rev 2016; Leopoldino et al. Cochrane Database Syst Rev 2019*). The effectiveness of non-surgical procedures such as epidural steroid injections and radiofrequency ablation, and surgery for chronic pain is also characterized by high failure rates, with most high quality studies showing no long-term benefit (*Foster et al. Lancet 2018; Juch et al. JAMA 2017; Cohen and Raja. Pain. Cecil Textbook of Medicine, 2019; Cohen et al. BMJ 2017; Hooten and Cohen. Mayo Clin Proceed 2015*).

For some opioid alternatives (e.g. NSAIDs in the elderly with co-morbid medical conditions, complex surgeries), the number-needed-to-harm for opioids is greater than for other treatments (i.e. safer). As another example, acetaminophen can cause liver toxicity in high doses

for certain individuals. According to the Dept. of Health and Human Services report on pain management best practices, the absence of robust data on the duration of opioid effectiveness should not be misinterpreted as a lack of effectiveness (*U.S. Dept. of Health and Human Services Pain Management Best Practices Inter-Agency Task Force. Draft report on Pain Management Best Practices: Updates, Gaps, Inconsistencies, and Recommendations. Available at: https://www.hhs.gov/ash/advisory-committees/pain/reports/2018-12-draft-report-on-updates-ga*).

The vagaries of our medical system also influence treatment decisions. For example, many patients do not want procedural interventions such as injections and surgery, which have been criticized in medical journals and lay publications for overuse (*Frakt A, Skinner J. The Puzzling Popularity of Back Surgery in Certain Regions. NY Times, Feb 13, 2017; Oliveira et al. Cochrane Database Syst Rev 2019; Deyo and Mirza. Clin Orthop Relat Res 2006; Kaplan S. After Doctors Cut Their Opioids, Patients Turn to a Risky Treatment for Back Pain. NY Times, July 31, 2018*), and 3rd party payers will not always reimburse alternative treatments such as integrative medical treatments (e.g. acupuncture), injections, and expensive non-opioid medications still on patent protection without extensive paperwork and prior documented treatment failures.

VII. OPIOIDS

A. MECHANISMS OF ACTION

Opioids mimic the actions of endogenous opioid peptides by interacting with mu, delta or kappa opioid receptors, which are contained in the central nervous system (responsible for most the analgesic and euphoric effects) and peripheral receptors. The opioid receptors are coupled to G1 proteins, and binding results in the closing N-type voltage-operated calcium channels (decreasing conductance) and opening inwardly-rectifying potassium channels (increased conductance). This results in hyperpolarization and a reduction in neuronal excitability, which leads to pain inhibition. They also inhibit adenylyl cyclase, which reduces intracellular cAMP, which modulates the release of nociceptive neurotransmitters (e.g. substance P).

B. HISTORY

The drug opium, cultivated since antiquity for its medicinal and mood-altering properties, consists of the dried juice of the poppy plant. In fact, the name ‘opium’ comes from the Greek word for ‘juice’. Technically speaking, the word opiate refers to any drug derived from opium. This includes the 2 naturally occurring derivatives morphine and codeine, as well as the semisynthetic compounds like heroin and Dilaudid (hydromorphone). The term opioid is broader and includes any group of drugs, natural or synthetic, that possesses morphine-like properties. This includes morphine and heroin as well as newer, more potent drugs like fentanyl, which, because of the lower incidence of side effects, have to a large extent replaced the opiates in anesthesia. When administered correctly, with proper supervision and monitoring, fentanyl is one of the most effective analgesic agents, as it is devoid of many off-target side effects observed

with naturally-occurring opiates such as histamine release and central nervous system stimulation. For this reason, it is the most commonly used analgesic for surgery in the world.

The word narcotic originally referred to any morphine-like substance but is gradually becoming obsolete in medicine. This is because it has legal and regulatory meanings that apply to any controlled substance that can cause dependence.

As with other medications, opioids exert their analgesic effects by binding to naturally occurring receptors in the body. These receptors were first identified in 1973 by Pert and Snyder (*Pert and Snyder. Science 1973*), and shortly thereafter the endogenous (naturally occurring) opioid enkephalin was discovered. To date, many different types of receptors have been isolated. Together, these receptors mediate the wide range of effects seen with opioids.

Opioids have been used to treat pain, and recreationally, for thousands of years. The pendulum on opioid use has swung back and forth throughout the centuries. Major developments in its use for pain occurred in the 19th century, with morphine being extracted from opium in 1803, and the hypodermic needle being invented in the 1850's. In addition to its potent analgesic effects, the addictive risks of opioids have been realized for years, including the first detailed descriptions of addiction to morphine in the late 1800's, and the passage of the Harrison Narcotics Act in 1914, which was aimed at restricting use and taxing revenues from drug commerce after a surge in abuse in the early 1900's.

For most of the mid- to late 20th century, most physicians avoided the use of opioid for chronic pain for fears of addiction. In the 1970's, Marks and Sachar published a study finding that 32% of inpatients treated with opioids continued to experience severe pain, with another 41% experiencing moderate pain. Yet, a dose of over 75 mg of meperidine (< 10 mg morphine equivalents) was prescribed to only one patient. They concluded that most house staff physicians had many misconceptions about opioids, and tended to overexaggerate the risk of addiction (*Marks and Sachar. Ann Intern Med 1973*). Similar reports were published on the undertreatment of pain in vulnerable populations such as children, the elderly and trauma victims, with many studies advocating more liberal opioid use (*Howard RF. JAMA 2003, Neighbor et al. Acad Emerg Med 2004; Sittl et al. Schmerz 2000; Dalacorte et al. N Am J Med Sci 2011*).

The medical community's greater attention on treating pain, including by using opioids, predates defendants' marketing of the opioid medicines in this litigation, and in my opinion was driven by unmet clinical needs rather than pharmaceutical companies.

Pain management and research into acute and chronic pain increased in the 1970s and 1980s. Clinicians and researchers came to realize that untreated pain—including cancer pain, inpatient surgical pain, post-surgical acute pain, and chronic non-cancer pain—was an important issue that was not being adequately addressed by pharmacological and other forms of treatment available at the time. During this time, pioneers in this field came to view opioids as a safe and effective treatment option for pain in appropriately selected pediatric and adult patients with cancer and non-cancer-related pain (*Twycross RG. J Medical Ethics 1975; Br Med J 1975; Charache S. Arch Intern Med 1974; McCaffery and Hart. Am J Nursing 1976; Foley KM. Med*

Clin N Am 1982; Yaster & Deshpande. J Pediatr 1988; Bonica JJ. Advances in Pain Research and Therapy, Vol 2, 1979; Rationale for the Development, Therapeutic Use, and Clinical Program for Transdermal System (Fentanyl), JAN-MS-02908137). One of these articles published in February 1990 in 'Scientific American' by the renowned researcher Ronald Melzack (discoverer of the 'Gate Control Theory of Pain') was entitled 'The Tragedy of Needless Pain', in which Dr. Melzack wrote, "Morphine taken solely to control pain is not addictive". Hence, emphasis on the burden of under-treated pain, and the concept that it should be treated with opioids, originated in the medical community.

The rise in opioid use can be viewed as a consequence to:

1) The rise in reported chronic pain prevalence, which is mostly due to greater surveillance (*Carragee and Cohen. Spine (Phila PA 1976) 2009; Hsu and Cohen. J Pain Res 2013*), and demographic factors such as the aging of our population;

2) Greater access to information and communication (i.e. internet, greater patient engagement (*Mogull SA. AMWA Journal 2008*), patient and patient-support groups); and

3) Our culture's desire for immediate gratification (*Cohen SP. A World of Pain. Project Syndicate, March 26, 2014*). The rise in opioid use is not a stand-alone phenomenon, as the 1980's through the 2000's witnessed commensurate rises in injections and spine surgeries, which were similarly criticized in high-impact non-medical publications (*Deyo and Mirza. Clin Orthop Relat Res 2006; Manchikanti et al. Pain Physician 2016; Kaplan S. After Doctors Cut Their Opioids, Patients Turn to a Risky Treatment for Back Pain. NY Times, July 31, 2018*).

Several events preceded the rise in opioid use. These include:

- The federal government identified an 'unmet' need for better pain treatment, which served as the impetus to develop Duragesic (*Rationale for the Development, Therapeutic Use, and Clinical Program for Transdermal System (Fentanyl), JAN-MS-02908137*);
- A case series of 38 patients with non-cancer pain successfully with opioids in 1986 (*Portenoy and Foley. Pain 1986*);
- The U.S. Drug Enforcement Agency in 1990 took the position that clinicians should be knowledgeable about using opioids to treat pain, and should not hesitate to prescribe them when opioids are the best clinical choice (*Drug Enforcement Administration. Physician's manual: An informational outline of the Controlled Substances Act of 1970. US Department of Justice, Washington, DC, 1990*).
- A 1980 letter to the editor in the New England Journal of Medicine reporting an addiction rate of 0.03% in inpatients with acute pain treated with opioids (*Porter and Jick. N Engl J Med 1980*);
- A World Health Organization monograph on the under-treatment of acute and cancer pain, including the publication of the WHO analgesic step ladder that included the use of opioids (*World Health Organization. (1986). Cancer pain relief. World Health Organization. http://www.who.int/iris/handle/10665/43944*);

- Growing reports by internationally-renowned figures on the under-treatment of pain and the long-term consequences of such under-treatment (*Melzack R. Sci Am 1990; Woolf CJ. Nature 1983*);
- Mitchell Max, Director of the Pain Research Clinic in the pain and neurosensory mechanisms branch of the NIH National Institute of Dental and Craniofacial Research (NIDCR) and the President of the American Pain Society, published an editorial in Annals of Internal Medicine advocated the more liberal use of opioids to treat chronic pain (*Max MB. Ann Intern Med 1990*);
- The American Pain Society launched their 'Pain is the 5th Vital Sign' campaign in 1995;
    - This was adapted the Department of Veteran's Affairs in 1999 (*Health Care Advisory Board. Pain Management in the VA and the Private Sector. Washington, DC: The Advisory Board Company; 1998*)
- 'Pain management' questions were used in the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey, which has been used since 2006 by the Centers for Medicare and Medicaid Services (CMS) to guide decisions (*Adams J. Am J Public Health 2016*).
- The Joint Commission, whose accreditation is required for reimbursement, published standards for pain management that included monitoring of pain and addressing it. Their 101-page manual, issued in 2001, included the following excerpts (*Skeptical Scalpel. Mo Med 2016*):
    - In 1968, McCaffery defined pain as "whatever the experiencing person says it is, existing whenever s/he says it does. This definition emphasizes that pain is a subjective experience with no objective measures. It also stresses that the patient, not clinician, is the authority on the pain and that his or her self-report is the most reliable indicator of pain."
    - "Some clinicians incorrectly assume that exposure to an addictive drug usually results in addiction."
    - Table 6: "Common misconceptions about pain: Use of opioids in patients with pain will cause them to become addicted."
    - Page 17: "In general, patients in pain do not become addicted to opioids. Although the actual risk of addiction is unknown, it is thought to be quite low."
    - Page 38: "Long-acting and sustained-release opioids are useful for patients with continuous pain, as they lessen the severity of end-of-dose pain and often allow the patient to sleep through the night."
    - Page 67: Table 38. "Administer opioids primarily via oral or transdermal routes, using long-acting medications when possible."

Recognition of the burden of acute and chronic pain soon led to the inauguration of medical journals and lay publications devoted solely to addressing acute and chronic pain. Clinicians and researchers came to realize that untreated pain—including cancer pain, inpatient surgical pain, post-surgical acute pain, and chronic non-cancer pain—was an important issue that was not being adequately addressed by pharmacological and other forms of treatment available at the time. In 1977, George Engel introduced the biopsychosocial model of pain, which

postulated that biological, psychological and social factors contributed to the pain experience, and that chronic pain had extensive ramifications and included not only biological (i.e. detrimental changes in the peripheral and central nervous systems) effects, but also adverse psychosocial consequences (*Engel G. Science 1977; Woolf CJ. Nature 1983*). Thus, the movement to adequately treat pain, and the emerging view that opioids could play an important role in treating chronic pain, originated in the medical community.

C. APPROVAL AND REGULATION BY FEDERAL AUTHORITIES

As the federal agency charged with protecting the public's health by assuring the safety, effectiveness, and security of medications, the U.S. Food and Drug Administration (FDA) plays a critical role in overseeing opioid use. The FDA is responsible for approving new medications and reformulations, and writing labels, including indications, and must consider the needs of patients, input from providers, and relevant public health considerations.

The original Pure Food and Drug Act of 1906 was passed in response to the growing use of morphine in the patent medicines of the 1800s, particularly products targeting children. The 1938 Food, Drug, and Cosmetic Act (FDCA) built on framework by requiring manufacturers to test their products for safety in patients. In the 1962 Kefauver-Harris Amendments, the FDA was given further authority to ensure that medications demonstrated evidence of efficacy based on well-designed investigations prior to approval.

In the 1960s and 1970s, the FDA approved short-acting combination products such as oxycodone/acetaminophen (Percocet, 1976) and hydrocodone/acetaminophen (Vicodin, 1978). In the late 1980s and early 1990s, the FDA approved extended-release formulations of older opioid products, such as morphine (MS Contin in 1985). These medications were approved for pain, without reference to whether or not the pain was cancer or non-cancer-related, or acute or chronic (though the extended-release formulations were approved for individuals with continuous pain, who are opioid-tolerant and expected to have pain for "extended periods of time" (*Philips JK. Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use. 2017*).

Through enactment of the Controlled Substances Act (CSA) of 1970, Congress restricted the access to controlled substances to individuals and entities registered to manufacture, distribute, or dispense such products. The main reason for passing the CSA was to enable the United States to comply with the requirements of 2 international treaties. These treaties, the 1961 Single Convention on Narcotic Drugs and the 1971 Convention on Psychotropic Substances, setup a system for classifying controlled substances in accordance with scientific evidence based on the determination of a public health authority, which in the U.S. rests with the Secretary of Health and Human Services (HHS). The U.S. Drug Enforcement Agency, a unit of the Federal Bureau of Investigation, is charged with implementation of the regulations of the CSA. As such, it can impose criminal penalties. In practice, the enforcement of the CSA limits access to controlled substances and ensures accountability for properly prescribing certain medications.

The CSA places all regulated substances into one of 5 categories, or schedules. This classification is based on the substance's medical value, risks, and the potential for abuse or addiction. Schedule I is reserved for the most dangerous drugs with no recognized medical use, while Schedule V is for the least dangerous drugs. Most opioids are classified as schedule II substances, meaning they have medical benefits but a high potential for abuse. Exceptions include doses < 90 mg of codeine (schedule III) and tramadol (schedule IV).

As controlled substances, opioids are available only by prescription from a healthcare provider who has registered with the DEA. Controlled substances are also subject to other regulations such as no refills (for schedule II drugs), and the requirement for a written, faxed (in some populations) or electronically submitted and signed prescription.

In March 2009, the FDA required an ER/LA opioid class-wide Risk Evaluation and Mitigation Strategies (REMS) and laid out guidelines for the plan (*3/9/2009 FDA Press Release re: REMS (JAN-MS-00484776)*). Shortly after the FDA's Press Release, pharmaceutical companies began to organize an Industry-wide Working Group (IWG) and hold discussions to determine how to best set up class-wide REMS. The IWG met regularly throughout 2009 (*12/4/2009 IWG Public Meeting Slides (JAN-MS-00209873)*). The goal of the class-wide REMS was to ensure that ER/LA opioid medication benefits outweighed the risks and that prescribers, dispensers, and patients were aware of the risks and appropriate uses of opioids. The REMS would focus on provider and patient education and include a plan for monitoring those educational efforts.

By June 2009, the IWG and the FDA had met to determine the scope, method, and requirements for the class-wide REMS (*JAN-MS-00209873*). In October 2009, the FDA announced that it would re-open the comment period for the class-wide REMS, leading to expectations of delays in implementing the REMS (*10/19/2009 Email re reopening of comment period for REMS by FDA (JAN-MS-02001916)*). The IWG continued meeting with the FDA and other stakeholders (such as the DEA). By December 2009, the FDA had expressed frustration at the amount of time it was taking the IWG to develop the class-wide REMS (*12/4/2009 IWG Public Meeting Slides (JAN-MS-00209873); 12/8/2009 Email (JAN-MS-01127834)*). In response, in March 2010, Endo, King, Janssen, and Purdue notified the rest of the IWG that they would take the lead in developing the class-wide REMS (*3/19/2010 IWG Memo (JAN-MS-02569643)*). In April 2010, the FDA announced that it would develop its own proposed REMS. (*4/6/2010 Email re FDA Plan to Develop Independent REMS (JAN-MS-02605687)*). In June 2010, the FDA released its proposed REMS (*July 22, 2010 FDA Proposal for REMS Publication (JAN-MS-02233933)*).

While the IWG continued to develop the class-wide REMS requirements with the FDA, Janssen discussed an interim REMS for Nucynta ER (*8/17/2011 Email Chain re Nucynta REMS (JAN-MS-01047546)*). On August 25, 2011, the FDA approved the Nucynta ER interim REMS. (*8/25/2011 Nucynta ER Approval Letter (JAN-MS-02543460); Nucynta ER REMS (JAN-MS-03088737)*).

Meanwhile, the class-wide REMS, which applied to Duragesic and other long-acting opioids, continued to develop throughout 2011. The IWG was initially hopeful that the class-wide REMS would be approved in April 2012, but pushback from the FDA delayed the launch (*5/3/2012 Janssen Slide Deck (JAN-MS-00451390)*). By May 2012, the FDA expressed it would announce approval of the class-wide REMS in mid-June. A delay in June pushed this date back again (*6/15/2012 Email (JAN-MS-00700690)*). Finally, on July 9, 2012, the FDA approved the class-wide REMS. Nucynta ER joined the class-wide REMS, and its individual REMS became defunct (*7/9/2012 Nucynta ER Revised REMS Approval Letter (JAN-MS-00775728); Original Classwide REMS (JAN-MS-00935481)*).

D. TYPES OF OPIOIDS

As mentioned above, the word opiate refers to any drug derived from opium. The term opioid is broader and includes any group of drugs, natural or synthetic, that possesses morphine-like properties. This includes morphine and heroin as well as newer drugs like fentanyl. These synthetic drugs, which include fentanyl and tapentadol, were designed to mimic the analgesic effects of opioids, but avoid certain off-target side effects such itching and hypotension. For this reason, fentanyl is the most opioid used in anesthesia. Today, the terms 'opiate' and 'opioid' are often used interchangeably.

Efficacy vs. Effectiveness vs. Potency

Efficacy can be defined as the performance of an intervention under ideal and controlled circumstances, whereas effectiveness refers to its performance under "real-world" conditions. These terms differ from potency, which is a measure of drug activity expressed in terms of the amount required to produce an effect of given intensity. Two drugs can be similar in efficacy and effectiveness, but have different potencies, such that higher doses are needed for less potent drugs (e.g. 10 mg of oxycodone is roughly equivalent to 15 mg of morphine, and 100 mcg of fentanyl). The efficacy of pure mu agonists is similar for individual drugs, though the effectiveness might be different for different people based upon metabolism, the binding properties to different sub-receptors (mu-1, mu-2) and a person's ability to tolerate side effects, which can differ slightly based on the particular drug and route of administration.

E. ROUTES OF ADMINISTRATION

Opioids exert most of their analgesic effects via receptors residing in the central nervous system, with the contribution of peripherally-located opioid receptors to pain relief being a subject of controversy (*Stein C. Expert Opin Investig Drugs 2018*). To bind to receptors in the central nervous system, medications can be directly delivered spinally (epidurally or intrathecally), which are specialized procedures and for long-term use, require surgically implanted devices, or by reaching the brain from the bloodstream. There are many ways to achieve plasma levels of a medication: intravenously, orally (by mouth, through the gastrointestinal tract), transmucosally (i.e. absorbed through mucosal surfaces such as under the tongue, intranasally or rectally), and transdermally (which requires small molecules that are soluble in fat). There are advantages and disadvantages of the different routes. Although orally

is the most common route of administration, many patients cannot take pills, develop gastrointestinal side effects when medications are given by mouth, and forget to take pills that need to be taken every day, often several times. The transdermal route of delivery has been approved for well over a dozen medications. Advantages include tolerability in individuals who are unable to tolerate oral preparations, better compliance, especially in the elderly and cognitively impaired, limited first-pass metabolism (i.e. the concentration of orally administered medications are decreased, by varying and sometimes unpredictable degrees, by metabolism by the liver), less gastrointestinal side effects, and less fluctuations in blood levels (*Isaac and Holvey. Ther Adv Psychopharmacol 2012*). Since some gastrointestinal side effects of opioids such as constipation are mediated locally (i.e. through mu receptors in the gut), transdermal fentanyl has been shown to have a lower incidence of constipation, and in some causes nausea and vomiting, than oral preparations (*Staats et al. South Med J 2004; Ackerman et al. Consult Pharm 2004; Allan et al. BMJ 2001; Allan et al. Spine (Phila PA 1976) 2005; Donner et al. Pain 1996; Wang et al. J Cancer Res Ther 2018*). For many patients, this superior side effect profile has translated into improved satisfaction and quality of life (*Allan et al. BMJ 2001; Allan et al. Spine (Phila PA 1976) 2005; Donner et al. Pain 1996; Wang et al. J Cancer Res Ther 2018*).

F. ABUSE-DETERRENT OPIOIDS

Given the concerns of abuse, the FDA has encouraged manufacturers to develop formulations that make abuse more difficult or less rewarding, and has issued several guidelines on this (*Abuse-deterrent opioids — evaluation and labeling guidance for industry [Internet]. Silver Spring (MD): FDA/CDER; 2015. Available from: https://www.fda.gov/ucm/groups/fdagovpublic/@fdagov-drugs-gen/documents/document/ucm334743.pdf; General principles for evaluating the abuse deterrence of generic solid oral opioid drug products guidance for industry [Internet]. Silver Spring (MD): FDA/CDER; 2017. Available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagovdrugs-gen/documents/document/ucm492172.pdf*). Abuse deterrent formulation strategies and technologies include physical and chemical barriers, agonist/ antagonist combinations, drug delivery technology, new molecular entities, the use of prodrugs, and aversion technologies (*Haddox JD. J Opioid Manage 2017*). It is important to note that these formulations do not prevent all types of abuse (i.e. take more pills or applying more patches than prescribed), but have been shown in multiple studies to prevent certain types of tampering and lower the risk of overdose (e.g. crushing pills to snort or inject); hence, they are not "abuse-proof" (*Kumar et al. Value Health 2019; Pergolizzi et al. Curr Med Res Opin 2018; Kopecky et al. J Clin Pharmacol 2017; Lamb et al. Drugs 2016; Bannwarth B. Drugs 2012*). As the FDA notes on its website: "Abuse-deterrent formulations target the known or expected routes of abuse, such as crushing in order to snort or dissolving in order to inject, for the specific opioid drug substance. The science of abuse deterrence is relatively new, and both the formulation technologies and the analytical, clinical, and statistical methods for evaluating those technologies are rapidly evolving. The FDA is working with many drug makers to support advancements in this area and helping drug makers navigate the regulatory path to market as quickly as possible. In working with industry, the FDA is taking a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products." (*U.S. Food and Drug Administration. Abuse-*

Deterrent Opioid Analgesics. Available at: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/abuse-deterrent-opioid-analgesics).

G. SUSTAINED-RELEASE OPIOIDS PLAY AN IMPORTANT ROLE IN TREATING CHRONIC NON-CANCER PAIN

The rationale for sustained release and long-acting (e.g. methadone, buprenorphine) opioids is grounded in the concept that approximately two-thirds of chronic pain patients have constant pain which requires sustained blood levels of analgesics above the therapeutic threshold (*Kennedy et al. J Pain 2014*). In this context, long-acting opioids better sustain therapeutic blood levels without the peaks and troughs, and peak blood levels (including the rate of rise) are associated with greater adverse effects, including euphoria. There are multiple articles by well-recognized experts that espouse this view, and contend that less euphoria can lead to less abuse and diversion (*McCarberg and Barkin. Am J Ther 2001; Heit HA. Eur J Pain 2001; Way et al. Basic & Clinical Pharmacology 8th ed. Opioid Analgesics & Antagonists 2001*). Medication adherence is also better for long-acting medications, which is particularly important in individuals with cognitive dysfunction, who are on multiple medications, and who have busy lifestyles. The argument that long-acting or sustained-release opioids provide less peaks and troughs is not only intuitive, but has been shown in pharmacokinetic studies. This is illustrated in a graph taken from McCarberg and Barkin (*Am J Ther 2001; figure 1*). Experimental studies performed in human volunteers have documented a correlation between serum opioid blood levels and both pain relief and respiratory depression, including for fentanyl (*Hill et al. Pain 2000*). Although the evidence for superior analgesia regarding long-acting opioids is conflicting (*Rauck R. Pain Pract 2009*), some randomized studies have found better analgesia for sustained-release opioids (*Ferrell et al. Onc Nurs Forum 1989; Hale et al. Pain Res Manage 1997*). This suggests that there may be a subset of patients who benefit (i.e. those with the most consistent pain).

Whereas the evidence in favor of better pain relief with sustained-release opioids has been characterized by researchers as weak (*Rauck R. Pain Pract 2009*), there are several advantages that have been documented in randomized trials. These include improved sleep, which is a finding that has external validity considering the duration of action for short-acting opioids is less than the typical person sleeps at night (*Caldwell et al. J Rheumatol 1999*), being less tired (which is consistent with the well-documented finding that side effects correlate with peak blood levels; *Klepstad et al. Pain 2003*), and patient and nurse preference (*Arkinstall et al. CMAJ 1989*). Studies have also found that sustained-release opioids such as the q3-day Duragesic formulation may improve treatment compliance, particularly in vulnerable populations such as the elderly and cognitively impaired (*Argoff and Silvershein. Mayo Clin Proceed 2009*).

CDC Guidelines and Evolving Views on Pain Management

In the 2016 CDC guidelines (*Dowell et al. MMWR (Mar. 18, 2016) and Errata (Mar. 26, 2016)*), the authors asserted that ER opioids were not more effective or safer than IR opioids, or that time-scheduled use reduced the risk of misuse or addiction. They also asserted that initiating treatment with ER opioids was associated with a higher risk of overdose than initiating treatment

with IR opioids, and in 2014 the FDA modified the labeling for ER/long-acting opioids, recommending that these medications be reserved for "management of pain severe enough to require daily, around-the-clock, long-term opioid treatment when alternative treatment options (e.g. non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain, and that they should not be used as 'as-needed' pain relievers. The FDA also stated that some ER/LA opioids are only appropriate for opioid-tolerant patients, which they defined as > 60 oral morphine or > 30 oral oxycodone equivalents per day.

However, the study that suggested a higher risk of overdose with SR opioids and led to the recommendation appeared in 2015 (*Miller et al. JAMA Intern Med 2015*), and the FDA did not change their labeling until 2014. The CDC guidelines grouped ER and long-acting opioids together, but noted that methadone (the only long-acting pure opioid agonist), which carries a higher risk for overdose and death than other opioids (*Faul M, Bohm M, Alexander C. MMRW March 13, 2017*) should not be a first-line choice for an ER/LA formulation. They also acknowledged that the pharmacodynamics and pharmacokinetics of transdermal fentanyl are often misunderstood by patients and physicians, and that physicians should educate patients on its use before prescribing it. Unlike methadone, which because of a half-life that is variable and may exceed 24 hours, can result in blood levels that continue to escalate for one week or more (it takes 5 half-lives to reach steady-state), ER formulations are inherently safer in that they do not result in rising and unpredictable blood levels when initiated.

For the reasons above, it is my opinion that the use of sustained-release opioids is based on logical, time-proven assumptions (better compliance, pharmacokinetics that conform to individuals with around-the-clock pain, less euphoria from lower peak levels). Applying data arrived from after-market studies retroactively is unfair and unjustified, akin to applying 2019 standards of care to conduct by physicians and other health care providers decades or centuries earlier.

H. DEFINITIONS

There are distinct differences between addiction, dependence, tolerance, and related terms, which are often misinterpreted and may overlap. Addiction is a neurobiological disease characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Although it is often characterized as a "disease", it does not fit the true medical definition of the term, which is "a distinct pathophysiological response to internal or external factors. In the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM 5), there is no diagnosis of 'opioid addiction'; rather, the term is more correctly denoted as 'opioid use disorder'. Unlike diseases, which have discrete pathophysiological mechanisms, that can often be replicated in preclinical models, and typically have well-defined and delineated criteria (e.g. positive sputum cultures and a positive chest x-ray for pneumonia, a fasting blood glucose > 120 for diabetes, specific autoantibodies for autoimmune diseases), there is generally a lot of ambiguity around the diagnosis of disorders or syndromes.

Abuse is the intentional use of a substance for a non-medical purpose, such as euphoria or altering one's state of consciousness. People can abuse medications for recreational purposes, but not be addicted. In contrast, misuse is characterized by use contrary to the directed or prescribed pattern of use, regardless of the presence or absence of harm or adverse effect. Patients may misuse opioids because they have worsening pain (e.g. taking 2 pills instead of one) or because they are unaware of physician guidelines (e.g. imbibing alcohol despite physician precautions not to).

Physical dependence is a state of adaptation that is manifested by a medication class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, or administration of an antagonist. Patients may be physically dependent on a medication without abusing it, or may abuse a medication that they are not physically dependent on. Tolerance is a state of adaptation in which exposure to a medication induces changes that result in a diminution of one or more of the medication's effects over time.

I. EVOLUTION OF GUIDELINES TO TREAT CHRONIC PAIN

1. Procedures

Epidural injections, first described in 1888 as a treatment for masturbation (*Corning L. Medical Record 1888*), have been used to treat back pain since the turn of the 20th century, with steroids being added in the early 1950's (*Sicard A. Compt Rend Soc De Biol 1901; Cathelin F. Compt Rend Soc De Biol 1901; Lievre J, Bloch-Michel H, Pean G, et al. L'hydrocortisone en injection locale. Rev Rhumat Mal Osteoartic 1953*). In the late 1950's, radiofrequency ablation to alleviate pain began to be used in neurosurgery, with its use to treat back pain being described in the early 1970's (*White et al. Trans Am Neurol Assoc 1959; Shealy CN. J Neurosurg 1975*). Neuromodulation evolved shortly after the groundbreaking description of the gate control theory of pain in 1965 (*Melzack and Wall. Science 1965*), being employed peripherally at first, followed in 1967 by the first description of spinal cord stimulation (*Wall and Sweet. Science 1967; Shealy et al. Anesth Analg (Clev) 1967*). Today, all of these procedures continue to be used, but remain mired in controversy regarding overuse and the risk-benefit ratio.

2. Non-Opioid Pharmacological Treatment

The treatment of chronic pain has evolved over the past 50 years. In the 1950's, the treatment of chronic pain was mostly limited to NSAIDs and acetaminophen, with opioids used only very sparingly. Antidepressants began to be systematically shown to be effective for chronic pain in the early 1960's after anecdotal reports emerged in the 1950's of them providing pain relief to depressed patients (*Lance JW, Curran DA. Lancet 1964*). The first use of anticonvulsants to treat neuropathic were in the 1940's with phenytoin being used to treat trigeminal neuralgia (*Ryder and Stannard. Br J Anaesth 2005*). Because adjuvants such as antidepressants, anticonvulsants and antiarrythmics exert their actions by depressing segments of the central nervous system, they are all characterized by side effects that include sedation and cognitive impairment. Despite the long history of use and multiple guidelines recommending them for chronic pain, FDA approval for the first antidepressants for chronic pain did not occur

until 2004. Although the FDA approved carbamazepine for trigeminal neuralgia in 1968 under orphan drug designation, gabapentin was not approved until 2002. In the interim, dozens of anticonvulsants and antidepressants were unsuccessfully trialed for chronic pain in humans. As noted above, these adjuvants typically alleviate less than half of a person's pain in a small minority of individuals.

3. Opioids

Approximately one-third of people with neuropathic pain receive substantial pain relief with adjuvants (defined by the IMMPACT guidelines as 30% or greater improvement; *Dworkin et al. J Pain 2008*), which has led to the search for more effective agents to treat both neuropathic and non-neuropathic pain (*Moore et al. Cochrane Database Syst Rev 2014; Lunn et al. Cochrane Database Syst Rev 2014*). Given the growing emphasis on the burden and consequences of chronic pain, the inherent limitations of the existing non-opioid treatments, and the burgeoning reports of their effectiveness in refractory pain, the healthcare community understandably began to turn to opioids for chronic pain patients desperate to alleviate their suffering. Starting in 1997 when a joint consensus statement by the American Pain Society and the American Academy of Pain Medicine developed guidelines for the use of opioids to treat chronic non-cancer pain (*A Consensus Statement from the American Academy of Pain Medicine and the American Pain Society. Clin J Pain 1997*), numerous other organizations recommended the judicious use of opioids in various contexts for the treatment of non-cancer pain in patients who failed other treatments. These include but are not limited to:

- The Federation of State Medical Boards in 1998 (updated in 2017, https://www.fsmb.org/siteassets/advocacy/policies/opioid_guidelines_as_adopted_april-2017_final.pdf);
- American Society of Interventional Pain Physicians in 2006 and 2008 (*Trescot et al. Pain Physician 2006 and 2008*);
- British Pain Society and other UK Professional Organizations in 2004 (*British Pain Society. Recommendations for the appropriate use of opioids for persistent non-cancer pain. A consensus statement prepared on behalf of the Pain Society, the Royal College of Anaesthetists, the Royal College of General Practitioners and the Royal College of Psychiatrists. London, UK: The British Pain Society; 2004*);
- U.S. Dept. of Veterans Affairs & U.S. Dept. of Defense in 2003 (*The Management of Opioid Therapy for Chronic Pain Working Group. VA/DoD Clinical Practical Guidelines for the management of opioid therapy for chronic pain. Contract Number: V101 (93)P1633(version 1.0). 2003*);
- Canadian Pain Society in 2002 (*Jovey et al. Pain Res Manage 2003*);
- Australian Pain Society in 1997 (*Graziotti et al. Med J Aust 1997*);
- Canadian Medical Association in 2010 (*Furlan et al. CMAJ 2010*);
- Utah Department of Health (*Utah clinical guidelines on prescribing opioids for treatment of pain. Salt Lake City (UT): The Department; 2009*).

It is important to note that these guidelines are not, and were never meant to be rigidly applied, but rather to be one part of an individualized, patient-focused approach.

VIII. OPIOIDS FOR NON-CANCER PAIN

All chronic diseases can adversely impact quality of life across multiple domains, and studies evaluating pain treatments should measure multiple metrics including function, psychosocial functioning, sleep, medication and healthcare utilization, etc. (*Turk et al. IMMPACT recommendations. Pain 2003; Christensen et al. Neurosci Biobehav Rev 2019*). People with poorly treated chronic pain are at higher risk of divorce, unemployment, depression and other psychological conditions (*GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Lancet 2018; Vieira et al. Cad Saude Publica 2012*). A recent cohort study conducted in nearly 7000 patients found that chronic non-cancer pain was associated with increased 10-year mortality independent of socio-demographic factors (*Torrance et al. Eur J Pain 2012*). This is similar to findings observed in cancer patients (*Staats et al. Pain Med 2001*). These facts underscore the medical necessity of effectively treating chronic pain.

A. GENERAL PRACTICES FOR TREATING NON-CANCER PAIN

Although pain is subjective, physicians and other health care providers can reasonably be expected to take steps to confirm the existence and severity of a patient's reported pain before prescribing opioid medications. These methods are reliable though not fool-proof, and include but are not limited to, a detailed medical history and physical exam, review of diagnostic information including imaging, and in-person discussions with the patient that include validated rating scales. Physicians who prescribe opioids to treat non-cancer pain receive education and training regarding these methods of assessing the existence and severity of reported pain.

The treatment of non-cancer pain has evolved over time. Physicians attempt to find out the underlying cause, previous past treatments and their effectiveness, other medical conditions that could impact treatment, and psychological and social factors that can influence treatment adherence and outcomes. Factors that affect which treatments to use include diagnosis, the severity of pain, the acuity and expected duration of the pain, patient desires and likelihood of adherence, physician determination of relative risks and benefits, and the impact of pain on the patient's health and well-being.

Treating chronic non-cancer pain is a collaborative process between physician and patient. This process should involve the development of a treatment plan that reflects reasonable goals and expectations of treatment. As a result, deciding whether and how to treat a patient's chronic non-cancer pain entails a thorough and individualized assessment.

Improving function is an important goal of treatment but it is not the only goal; mere reduction of pain can improve quality of life. In addition, "function" is a broad term in practice that depends on patient-specific factors including age, daily activities, capabilities, goals, employment status, and other medical conditions. For this reason, "function" is difficult to assess across patients using a single metric.

B. REASONS FOR PRESCRIBING OPIOIDS: PRECISION MEDICINE

There are many reasons for prescribing opioids as a class. Unlike non-steroidal anti-inflammatory drugs and some adjuvants (e.g. ketamine, tricyclic antidepressants), opioids have no end-organ toxicity, which makes them an ideal medication in patients with multiple co-morbidities. As noted above, even for neuropathic pain, the NNT for opioids is lower or comparable to most first-line medications (*Finnerup et al. MedGenMed 2007; Finnerup et al. Lancet Neurol 2015*); for certain central pain conditions, opioids are one of the few drugs with proven efficacy in multiple randomized controlled trials (*Wu et al. Anesthesiology 2002; Wu et al. Anesthesiology 2008; Siddall et al. Anesth Analg 2000; Norrbrink and Lundeberg. Clin J Pain 2009*).

The most widely acknowledged definition of evidence-based medicine includes not only consideration of the results of clinical trials, but also takes into account physician judgment and patient preference (*Sackett et al. Clin Orthop Relat Res 2007*). Precision medicine incorporates individual characteristics and priorities to come up with a personalized treatment plan. Although the risks of opioid therapy may outweigh the benefits in certain populations (e.g. young individuals with multiple psychiatric risk factors), in others the potential benefits of opioids clearly outweigh the risks (e.g. an elderly person with osteoarthritis who has a history of renal and cardiovascular disease and is faced with the choice of a trial with opioids or multiple joint replacement surgeries after failing conservative therapy).

1. Problems With Opioid Tapering

Statistics measuring the benefits of opioids for chronic pain are more difficult to assess. How does one measure subjective benefits, or balance them against risks? What value does society place on a caregiver being able to support their family? How does one quantify cost savings in people who are less depressed, able to function better, and undergo less treatments? Because people with poorly treated pain are at high risk for suicide (*Lewcun et al. Psychol Serv 2018*) and frequently undergo risky and unproven treatments that can drain savings, the alleviation of otherwise refractory pain can save lives. The surge in suicides and other harms in individuals who were forcibly tapered off 'life-saving' opioids is real, but rarely appreciated (*Ilgen M. Ann Intern Med 2018; Stonington and Coffa. N Eng J Med 2019; Llorente E. As doctors taper or end opioid prescriptions, many patients driven to despair, suicide. Fox News, December 10, 2018. Available at: https://www.foxnews.com/health/as-opioids-become-taboo-doctors-taper-down-or-abandon-pain-patients-driving-many-to-suicide*). In one early randomized, double-blind, placebo-controlled trial that substituted placebo for morphine in patients on sustained-release morphine, following cessation and abstinence, the 10 participants experienced detrimental effects on pain, activity levels, mood, and quality of life (*Cowan et al. Pain Med 2005*). These results were confirmed in a more recent study involving 49 patients who wanted to taper off opioids, and had been opioid-free for a median duration of 9 months. In this study, > 50% more individuals experienced worsening pain than improved pain, and nearly twice as many people had poorer function than those who reported improved ability to perform activities of daily living (*Goesling et al. Pain 2019*). These results are important because the

amount of time these individuals had been off opioids indicates that worsening pain from 'opioid-induced hyperalgesia' would be unlikely to explain the results.

2. Opioid-Induced Hyperalgesia: Fact or Fiction

The concept of opioid-induced hyperalgesia (OIH) has been postulated for more than a century (*Raffa and Pergolizzi. Pain Manag Nur 2013*). It refers to the phenomenon whereby exposure to opioids, usually involving high doses over prolonged periods of time, causes sensitization of nociceptors, thereby producing a paradoxical response in which a person receiving opioids could actually become more sensitive to certain painful stimuli (*Lee et al. Pain Physician 2011*). Clinically, it can extremely difficult or impossible to distinguish between OIH, tolerance and 'disease progression'. Perhaps the best way to clinically differentiate opioid tolerance from OIH is a trial of opioid weaning—if pain improves after the receptors have had a chance to reset, then OIH is suspected, whereas persistent worsening pain suggests tolerance (*Crooks M, Cohen SP. Managing opioid hyperalgesia in the perioperative period. In: Mao J, ed. Opioid Hyperalgesia. New York: Informa, 2009; Tawfic et al. Sultan Qaboos Univ Med J 2013; Tompkins and Campbell. Curr Rev Headache Rep 2011*).

The studies supporting the concept derive mostly from experimental studies in human volunteers without pain (which tend to translate poorly to clinical studies and practice), patients on methadone or buprenorphine because of addiction (which limits generalization) and clinical studies showing that opioids given during surgery result in increased postoperative pain (which are inherently flawed since surgery cannot be controlled) (*Tompkins and Campbell. Curr Rev Headache Rep 2011; Rafa and Pergolizzi. Pain Manag Nurs 2013; Lee et al. Pain Physician 2011*).

The clinical evidence supporting opioid hyperalgesia is mixed, and mostly limited to the perioperative pain context. In a meta-analysis that examined 27 studies and 1494 patients, Fletcher and Martinez found a small effect whereby individuals who received high-dose intraoperative opioids reported higher pain scores and had higher opioid consumptions postoperatively. However, there were many studies, and parts of studies, that did not support the concept of opioid hyperalgesia, and the studies were mostly limited to remifentanil, leading the authors to state, "the impact of other opioids is less clear (on OIH) because of limited data." (*Fletcher and Martinez. Br J Anaesth 2014*).

For chronic pain, the evidence is even more nebulous. In one of the only large-scale, prospective clinical studies evaluating the effect of opioid dose on clinical pain perception, we found a small effect whereby higher doses of opioids were associated with higher pain ratings for a standardized clinical stimulus administered (local anesthetic injection) before a pain management procedure (*Cohen et al. Reg Anesth Pain Med 2008*). However, this study did not establish a cause and effect relationship, such that it was impossible to determine whether higher doses of opioids caused increased pain sensitivity, or individuals with increased pain sensitivity required higher doses of opioids. In the more recent Goesling et al. study, a significantly higher percentage of patients on chronic opioid therapy who voluntarily tapered off (median duration of stoppage 273.6 days) because they wanted to do so reported more pain and poorer function after

discontinuation of opioid therapy (*Goesling et al. Pain 2019*). In another study that examined interruptions in opioid therapy due to acute illness among nursing home patients with chronic pain, Redding and colleagues found that opioid cessation was associated with worsening pain in a significant proportion of patients, with those on the highest doses experiencing the greatest increase in pain (*Redding et al. Clin Ther 2014*). As a consequence of these findings, numerous narrative and systematic reviews have questioned the clinical significance of the phenomenon (*Rafa and Pergolizzi. Pain Manag Nurs 2013; Fishbain et al. Pain Med 2009; Reznikov et al. Br J Clin Pharmacol 2005; Harper DC. Prac Pain Manage 2010; Higgins et al. Br J Anaesth 2018*). In summary, the evidence supporting OIH derives predominantly from preclinical and acute pain studies, but its clinical significance is unclear, especially in a chronic pain context.

C. BALANCING RISKS AND BENEFITS

Every medical treatment contains the potential for risks and benefits, and these need to be weighed for individual patients. For example, in a reliable elderly person with coronary artery disease, no psychiatric illnesses, no family history of substance abuse, and a strong social network who has failed conservative therapy for debilitating knee osteoarthritis (e.g. knee injections, non-steroidal anti-inflammatory drugs), the use of opioids almost certainly carries less risks than joint replacement. For a young smoker with depression and back pain, the relative risks may be different.

Opioids have been a cornerstone of pain treatment for millennia, and there is little controversy on their benefits for acute pain. Yet, the mechanisms underscoring acute and chronic pain are very similar (i.e. there are no separate pain pathways), such that most medications for acute pain have been used to treat chronic pain and vice versa (e.g. ketamine for chronic pain, intrathecal therapy with opioids and other analgesics, gabapentin and antidepressants to reduce acute pain, non-steroidal anti-inflammatory drugs for acute and chronic pain; *Richebe et al. Anesthesiology 2018; Cohen et al. Reg Anesth Pain Med 2018; Deer et al. Neuromodulation 3027*).

Opioids carry well-known risks, but are generally more effective than some other pain treatments for a wider range of pain conditions. For example, non-steroidal anti-inflammatory drugs are considered to be ineffective for neuropathic pain, and first-line adjuvants for neuropathic pain such as gabapentin and pregabalin are ineffective for nociceptive pain (*Attal et al. Eur J Neurol 2010; Finnerup et al. Lancet Neurol 2015; Shanthanna et al. PLoS Med 2017*). Yet, opioids have been shown to alleviate all types of pain, in all types of people. As noted above, the statistics on opioid abuse and overdoses are easily tabulated and make powerful headlines; yet, statistics on the number of marriages, jobs and lives they have saved are less glamorous, and much more difficult to quantify.

The risk-benefit ratio of any treatment can be beneficially altered by more data and good judgment. A good history, including risk stratification, a frank discussion on expectations, goals and risks (e.g. informed consent) that includes family members, establishing clear benchmarks for defining success, monitoring for aberrant behaviors and objective measures of success (e.g.

functional capacity, pain relief), and an exit strategy, can dramatically alter the risk-benefit ratio (*Cohen and Raja. Nature Clin Pract Neurol 2006*).

The White House Office of National Drug Control Policy (ONDCP) sets the strategy for all federal agencies that address drug abuse in the United States via its annual National Drug Control Strategy (Office of National Drug Control Policy: Epidemic: responding to America's prescription drug abuse crisis. Available at https://www.whitehouse.gov/sites/default/files/ondcp/policyand-research/rx_abuse_plan.pdf.). In 2011, ONDCP released a supplemental document that sought to curb abuse of prescription medicines based on four "pillars". These pillars are:

1. Education for prescribers and consumers;
2. Monitoring activities such as prescription drug monitoring programs and clinical monitoring of patient response;
3. Disposal programs such as take-back programs and FDA instructions in each product's label (package insert); and
4. Enforcement of existing laws against trafficking and pill mills.

These and other risk mitigation strategies (Risk Evaluation and Mitigation Strategies, a.k.a. REMS) as outlined in numerous FDA documents have been advocated by Johnson and Johnson and medical experts (including the individual and societies referenced in the lawsuits), but there are many obstacles to implementing them that are not often discussed. These include but are not limited to time constraints created by the growing administrative burdens faced by physicians, and greed by individual practitioners (e.g. quid pro quo whereby patients received opioids in exchange for allowing physicians to perform procedures on them; toxicology labs owned by prescribers of opioids).

1. Prescribing Opioids in Practice

The setting for the evaluation of pain and physician referral patterns (i.e. where patients are sent) can have substantial effects on treatment decisions. The evaluation of the chronic pain patient for the Johns Hopkins Blaustein Pain Treatment Center and many other pain clinics in private practice and academia begins with screening, which is often done by non-physicians who special services. This screening should ideally notify patients about requirements (e.g. referral from a physician, relevant past medical records from other providers), and policies of the clinic (e.g. we do not see patients with 'such and such' conditions, all patients must have a primary care provider, we do not typically takeover opioid prescriptions from other doctors, or we do not prescribe opioids on a first visit).

When the patient comes in for their evaluation, a detailed history and physical exam is performed, which includes concomitant medical and psychiatric conditions, current medications, past treatments tried, and the results of those treatments. For individuals with back pain (which is the most complaint among chronic pain patients in civilian and military treatment facilities, *Odonkor et al. Anesth Analg 2016; Cohen et al. Anesth Analg 2005*) and other conditions, many practitioners seek to identify signs of non-organic pathology that could result in the decision to send the patient for a psychological evaluation, and influence whether or not an injection is

scheduled (*D'Souza RS, Law L. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019*). A diagnosis, or differential diagnosis, is rendered, with special attention as to whether or not the pain is neuropathic or non-neuropathic, since this classification affects treatment decisions at every level of care (*Chang et al. Curr Opin Anaesthesiol* 2015).

The decision as to whether or not to prescribe a medication, perform a procedure, or refer the patient to a different provider (e.g. surgeon, acupuncturist or other integrative medicine specialist, physical therapy, psychologist, rehabilitation doctor, sleep specialist) should ideally be based on a shared decision model that takes into account physician judgment, and patient characteristics that include preferences and access (i.e. prescribing expensive medications and other treatments such as integrative therapies that are not covered by insurance to patients who cannot afford them is likely to impede access to care and limit adherence). For many brand name, integrative (e.g. acupuncture, spinal manipulation, Tai Chi, yoga) and interventional treatments, insurance authorization tends to be less reliable than opioids and generic non-opioid medications (*Lin et al. JAMA Netw Open 2018*). This is because opioids such as Duragesic and Nucynta tend to have more general indications (i.e. "pain severe enough to require around-the-clock… alternative treatment options are inadequate"), while many other medications (e.g. Lyrica, duloxetine) have specific, disease-based indications that often exclude common conditions such as sciatica, persistent postsurgical pain and complex regional pain syndrome. In general, guidelines typically recommend a stepped care approach similar to that employed in the Veterans Health Administration (*Available at: https://www.research.va.gov/research_in_action/Stepped-care-and-collaborative-care-models-for-chronic-musculoskeletal-pain.cfm*), with more conservative therapies being utilized before more invasive and riskier treatments. For non-neuropathic pain, first-step treatments might include physical therapy, NSAIDs and muscle relaxants, the latter of which can be associated with significant risks and side effects. For neuropathic pain, these may include antidepressants and anticonvulsants, both of which depress the central nervous system. Interventional treatments that can be considered when first-tier treatments fail include steroid injections and radiofrequency ablation for joint pain, and epidural steroid injections and pulsed radiofrequency for neuropathic pain. None of these treatments are devoid of risk, and most provide benefit to only a minority of individuals (*Bicket et al. Pain Manag 2015; McAlindon et al. JAMA 2017; Cohen and Raja. Anesthesiology 2007*).

In individuals who fail conservative treatment, the decision if and when to prescribe opioids must be tailored individually to each patient (personalized medicine), as not all patients are candidates for opioid therapy or want it. Factors that weigh into this decision include the impact of pain on a person's quality of life, the evidence supporting opioids for the particular diagnosis, the compliance and reliability of the patient, and risk stratification, for which several instruments exist (*Jan SA. J Manag Care Pharm 2010*). The multiple guidelines that recommend opioid therapy for chronic pain all assert that they be used judiciously, not indiscriminately. When opioid therapy is considered, there are a number of tools that can be used to minimize risks and optimize outcomes including obtaining informed consent, the signing of an opioid contract delineating the expectations and responsibilities of all parties, random drug testing, identifying realistic goals with specific benchmarks, the development of an exit strategy, and

frequent evaluation to ensure compliance and continued effectiveness (*Wyse et al. Pain Med 2018*). Several well-designed randomized studies have also found increased benefit when opioids are combined with NSAIDs and adjuvants (*Chaparro et al. Cochrane Database Syst Rev 2013*). In large healthcare systems, the judicious use of opioid for chronic pain has successfully been employed within the stepped care model (*Moore et al. J Rehabil Res Dev 2016; Dorfinger et al. J Gen Intern Med 2014*).

2. Opioids for Neuropathic Pain

For many years, it was asserted that opioids were less effective for neuropathic pain than for nociceptive pain (*Arner and Myerson. Pain 1988*; *Portenoy et al. Pain 1990*), but high-quality research in the form of randomized controlled trials from renowned sources such as Howard Fields determined that opioids are effective for the latter (*Fields HL. Pain 1988; Rowbotham et al. Neurology 1991*). In some, including one published in the New England Journal of Medicine, the authors asserted that higher opioid doses were more effective than lower doses (*Rowbotham et al. N Engl J Med 2003*). Placebo-controlled trials have also found opioids effective for nociplastic conditions such as fibromyalgia (*Bennett et al. Am J Med 2003*) and complex regional pain syndrome (*Simpson et al. Clin Ther 2007*). In fact for neuropathic pain, the number-needed-to-treat (NNT) for one person to obtain significant benefit above placebo is more favorable for opioids than for other medications. The NNT ranges from 3.5 to 11 for first- and second-line non-opioid adjuvants (7.2 for gabapentin, 7.7 for pregabalin, 3.6 for tricyclic antidepressants, 6.4 for serotonin-norepinephrine reuptake inhibitors (SNRI) and 10.6 for capsaicin 8%), but is consistently less than 5 for opioids (3.7 for morphine, *Cooper et al. Cochrane Database Syst Rev 2017*; 4.7 for tramadol, 4.3 for strong opioids, *Finnerup et al. Lancet Neurol 2015*); this indicates that opioids are more efficacious than nearly other medications for a condition—neuropathic pain—that is often considered less responsive to opioids. In the updated 2015 International Association for the Study of Pain Neuropathic Pain (IASP) Special Interest Group recommendations on the treatment of neuropathic pain, tramadol was considered to be a 2nd line agent, with stronger opioids recommended as 3rd line (*Finnerup et al. Lancet Neurol 2015*).

During the 2000's, the recommendations supporting opioids were even more emphatic. The comprehensive Swedish Council on Health Technology Assessment published in 2006 found that for neuropathic pain, opioids had the lowest NNT at 2.6 (i.e. were the most effective) and were equally effective as NSAIDS (the 1st line treatment) for osteoarthritis (*Swedish Council on Health Technology Assessment, 2006*). In 2007, the authors for the IASP recommendations found that opioids and tricyclic antidepressants were the most effective medications for treating neuropathic pain (NNT's between 2 and 3), providing better pain relief than 1st line agents such as gabapentinoids and SNRI (*Finnerup et al. MedGenMed 2007*). In the 2007 IASP guidelines, opioids and tramadol were recommended as 2nd line agents for neuropathic but could be considered 1st line in certain circumstances (*Dworkin et al. Pain 2007*).

D. PHYSICIANS HAVE KNOWN THE RISKS THAT OPIOIDS CARRY, INCLUDING ABUSE, ADDICTION, AND OVERDOSE

1. Physician Knowledge

In my opinion, any physician who prescribed opioids to treat chronic non-cancer pain knew or should have known of their risks at the time frame at issue in this litigation. To begin with, any doctor prescribing a medication should be aware of the content of the FDA-approved product labeling, which describes in detail the indications, dosing guidelines, warnings, precautions, potential contraindications, information related to special populations, information related to use during pregnancy, and other important information relevant to the prescribing decision. The labels for Duragesic, Nucynta, and Nucynta ER adequately disclosed these risks, and the labels were written in a language that should have been understood by those authorized to prescribe opioid medications.

In addition, physicians and others who treat chronic non-cancer pain are expected (and required in many contexts such as license renewal and board certification) to remain up-to-date with the standard of care and current medical knowledge regarding treating chronic non-cancer pain, the available treatment options, and the risks and benefits of those treatments. Physicians are expected to do so by reviewing publications and medical literature, attending meetings and programs, and discussing issues with colleagues, among other avenues.

I therefore disagree with the opinions of plaintiffs' experts Dr. David Kessler's and Dr. Anna Lembke's that physicians at issue in this litigation did not understand the risks associated with Janssen opioid medications. In my opinion, those prescribing Janssen medications had sufficient information available to them through their medical training, medical literature, FDA-reviewed labeling, and other sources to understand the medications' risks and benefits.

2. Primary Care Physicians

Most opioids are prescribed by primary care physicians, who are on the frontlines treating pain (*Guy and Zhang. Am J Prev Med 2018*). Pain is the leading reason people see a physician (*Sauver et al. Mayo Clin Proc 2013*), so primary care providers (PCP) should be familiar with the fundamentals of pain treatment.

The argument that PCPs are not capable of discerning the literature on opioids is spurious. No physician or healthcare provider, including nurse practitioners, dentists and other non-physicians, can prescribe opioids without being registered with the Drug Enforcement Agency, and this registration is voluntary. Most PCPs know their patients much better than specialists who may see them briefly for one or two visits, and therefore are best able to identify factors which would make them suitable or unsuitable (e.g. past substance use history, family history, unreliability, poor coping mechanisms in the context of a stressful job or personal life) for chronic opioid therapy. The assertion by Dr. Lembke that their educational background make them poorly qualified to assess pain and treat it is illogical. The scope of new knowledge is such that very little of what trainees learned even 15 years ago is operative today, so the burden of keeping up with medical advancements is incumbent upon the physician. In fact, the goals of

medical education include teaching students problem solving and critical thinking skills, how to access and interpret information, and how to apply these skills. All primary care and general medical journals publish articles on pain and opioids, and these issues are discussed at major conferences. There is no reason to think that PCPs are incapable of accessing, evaluating and applying new information on chronic opioid therapy for pain, or that chronic pain is somewhat unique as a symptom in that they do not know when these patients should be referred for specialty care.

E. DIFFERENCES BETWEEN CANCER & NON-CANCER PAIN ARE NOT PATHOPHYSIOLOGICAL

Chronic pain is often classified as cancer-related and non-cancer-related, with the diagnosis being histological. Opioids have justifiably been considered a cornerstone of cancer pain treatment for decades, preceding the current rise in medicinal use. In 1986, the World Health Organization developed an analgesic ladder for pain treatment in cancer patients, with opioids positioned at the top of the pyramid. The rationale for the use of opioids in cancer pain are that:

1) Patients have an indisputable source of (mostly nociceptive) pain, that is likely to progress over time;

2) Issues such as tolerance and hyperalgesia are less relevant in this population;

3) Cancer patients may be less likely to exhibit certain aberrant behaviors such as diversion.

Yet, the mechanisms underlying cancer and non-cancer pain are the same (i.e. the pain pathways are the same). This fundamental fact is noted in numerous scientific and lay articles, and evidenced by the fact that there are no specific "cancer-pain pathways" in the body (*Widera E. Chronic Cancer versus Non-Cancer Pain: A Distinction without a Difference? Available at: https://www.geripal.org/2016/03/chronic-cancer-versus-non-cancer-pain.html; Peppin and Schatman. J Pain Res 2016*). On page 237 of his deposition, Dr. Schumacher asserts that cancer pain differs from non-cancer pain by "releasing factors that produce plasticity". This is false. Neuroplasticity can be associated with any chronic pain condition, and in fact is more commonly linked to nociplastic and neuropathic pain than non-neuropathic pain (whereas cancer pain may have neuropathic qualities, especially in terminal cancer cases, it is classically considered to be nociceptive pain as only a minority of patients have demonstrable evidence of nerve damage) (*Gwak et al. Neural Plast 2017; Freynhagen et al. Curr Med Res Opin 2019; Meacham et al. Curr Pain Headache Rep 2017; Davis MP. Hematol Oncol Clin North Am 2018).* Among nociplastic pain conditions (e.g. fibromyalgia, irritable bowel syndrome), which are classically associated with neuroplasticity (hence the name), opioids are generally not recommended for their treatment (*Goldenberg et al. Mayo Clin Proceed 2016*), as many of these individuals tend to have elevated levels of endogenous opioid peptides (*Baraniuk et al. BMC Musculoskelet Disord 2004*).

With improved treatments, many cancers are not terminal, or are associated with long life expectancies, which can be very variable. In contrast, an elderly patient with diabetic neuropathy and osteoarthritis who has cardiovascular disease may have a shorter life expectancy than most people with cancer, and elderly people develop tolerance at a slower pace than younger individuals (*Zhao et al. Mol Pain 2012*). Moreover, some opioids decrease the immune response to cancer, and there is mixed evidence on whether or not they can adversely affect survival rate (*Boland and Pockley. Br J Pharmacol 2018*). Therefore, in my opinion the argument that opioids are reasonable for cancer pain, but unreasonable for non-cancer pain, is a specious one. The same underlying mechanisms imply that if opioids are effective in the long-term for cancer pain, they are also effective for non-cancer pain.

This view is supported by the FDA in its response to Dr. Andrew Kolodny, President of Physicians for Responsible Opioid Prescribing (PROP) on September 10, 2013 (Docket No. FDA-2012-P-0818). PROP had requested changes to the labeling of extended release/ long-acting opioids to restrict their use to cancer pain. The FDA wrote, "It is the FDA's view that a patient without cancer, like a patient with cancer, may suffer from chronic pain, and PROP has not provided any scientific support for why labeling should recommend different treatment for such patients. In addition, FDA knows of no physiological or pharmacological basis upon which to differentiate the treatment of chronic pain in a cancer setting or patient from the treatment of chronic pain in the absence of cancer… FDA therefore declines to make a distinction between cancer and non-cancer chronic pain in opioid labeling."

F. LONG-TERM EFFECTIVENESS OF OPIOIDS

Critics cite studies showing opioids are not more effective than other pain medications (*Smith et al. Osteoarthritis Cartilage 2016*), and argue that there is minimal evidence of long-term effectiveness (*Chou et al. Ann Intern Med 2015)*. Yet, these criticisms can just as easily be turned against non-opioids. A large proportion of patients on chronic opioids have failed other medications, or can't take them for safety reasons. Opioids have not been shown to be efficacious in placebo-controlled trials for chronic pain beyond 12 weeks, but neither have other analgesics. Even for cancer pain, they have not been studied in controlled settings for longer than 12 weeks. The reasons for this are complex, but include practical concerns such as the ethics of conducting studies in which patients receive a placebo for longer than the 12-week timeframe the FDA requires for approval.

This is noted by the FDA in their response to Dr. Andrew Kolodny and PROP on September 13, 2013, when they note why the FDA does not require placebo-controlled studies beyond 12-week follow-up (Docket No. FDA-2012-P-0818).

Similar to all chronic pain interventions including non-opioids, non-surgical interventions such as epidural steroid injections and radiofrequency ablation, and surgery, the benefits of chronic opioid therapy diminish with time. Yet, multiple open-label continuation studies have established the long-term effectiveness of opioids (*Arkinstall et al. Pain 1995*), including several studies for Duragesic (*Dellemijn et al. J Pain Symptom Manage 1998; Nugent et al. J Pain Symptom Manage 2001; Simmonds and Richenbacher. J Pain Symptom Manage 1992*) and

Nucynta (*Strick V. Curr Med Res Opin 2014; Baron et al. Pain Pract 2017*) and mixed mechanism opioids such as tapentadol (*Pascual et al. Curr Med Res Opin 2007; Buynak et al. Clin Ther 2015; Afilalo and Morlion. Pain Physician 2013*). In these studies, a substantial majority of patients who obtained relief at 3 months continued to experience comparable benefit at follow-up periods extending over 1 year. A recent systematic review and meta-analysis examining the health-related quality of life in patients receiving long-term opioid therapy demonstrated an improvement in physical functioning, but not mental functioning (opioids are not a treatment and are not advocated to treat psychological issues; *Thornton et al. Qual Life Res 2017*).

A recent study published by a well-known group of opioid researchers found unexpected results when they performed interviews on 49 patients who had stopped chronic opioid therapy a median 9 months earlier. Goesling et al. found that while 30.6% experienced an improvement in pain and 20% had improvement in physical function, 47% and 39% experienced worsening of pain and function, respectively (*Goesling et al. Pain 2019*).

G. CEILING EFFECT FOR OPIOIDS

I disagree with the view that Janssen has made misleading statements in materials cited by plaintiffs' experts regarding a "ceiling effect" for opioids. The assertion that there is no ceiling effect for opioids was not invented by manufacturers. Opioids are used to induce general anesthesia, and a review in 1987 states, "Both sufentanil and alfentanil are also used in cardiac anaesthesia. The newer agonist-antagonist opioids, butorphanol, nalbuphine and buprenorphine, have largely replaced pentazocine in clinical practice. Unlike pentazocine, they cause a low incidence of dysphoric side effects. Like the pure agonists, they cause respiratory depression; however, in contrast to the pure agonists this is not dose related, reaching a 'ceiling' as dose increases (*Bovill JG. Drugs 1987*)." A review on opioids by Rosenblum et al. funded by a grant from the National Institute for Drug Abuse (NIDA) states that "Those (opioids) with a low intrinsic activity are called partial opioid agonists and are characterized by a ceiling on most agonist activity, such that increases in dose will increase the drug's physiological and subjective effects only to a certain level and further dose increases produce no additional effects." (*Rosenblum et al. Exp Clin Psychopharmacol 2008*). The source for this was a book chapter in the world's most authoritative textbook on pharmacology, 'The Pharmacological Basis of Therapeutics' (*Jaffe JH, Martin WR. Narcotic analgesics and antagonists. In: Goodman LS, Gilman A, editors. The Pharmacological Basis of Therapeutics. New York: Macmillan; 1990).* This implies that pure agonists are devoid of a "ceiling" (Jaffe & Martin, 1990). In addition, the WHO analgesic stepladder for cancer pain management, originally published in 1986 and which was adapted for chronic pain, notes there are 'weak' and 'strong' opioids (steps 2 and 3, respectively), which should be used in succession after failure of non-opioid therapy (*World Health Organization (1986). Cancer pain relief. Geneva: World Health Organization*). This implies that weak opioids have a 'ceiling', which can be surpassed by stronger opioids. The concept that there is no ceiling effect has been supported by well-respected websites, such as Medscape (*Motov SM, Ast T. Is There a Limit to the Analgesic Effect of Pain Medications? Medscape, posted June 17, 2008. Available at: https://www.medscape.com/viewarticle/574279*).

The way many people interpret 'no ceiling' effect is that the dose necessary for pain relief is very different for different people, which is consistent with studies showing a poor association between opioid dose and pain relief (*Chen et al. J Pain 2013*). The "no ceiling" effect concept is also captured in the acute setting when many patients are titrated to analgesic effect without a predetermined dosing limit.

H. ADDICTION TO OPIOIDS

I disagree with the view that Janssen has made misleading statements in materials cited by plaintiffs' experts regarding the addiction rate or potential of opioids. The reported rate of addiction in the literature varies widely, from less than 1% to over 50%. The reasons for the wide variation include methodology (i.e. population, sample size, study design), definition, and bias. A 2010 Cochrane review found that there was a "very small (though not zero) risk of developing addiction, abuse, or other serious side effects," and concluded that the rates of addictive behaviors "do not support the contention that potential iatrogenic opioid addiction should limit therapy for well-selected and well-supervised patients" (*Noble et al. Cochrane Database of Systemic Review 2010*).

A 2015 systematic review published in 'Pain' found that estimates of misuse ranged from 21% to 29%, while those of addiction ranged between 8% and 12% (*Vowles et al. Pain 2015*). This review contained significant limitations including the reliance on studies in which the authors caution against such reliance (*Banta-Green et al. Drug Alcohol Depend 2009*), and the inability to control for the populations evaluated. In a review of reviews by Voon and colleagues, in addition to the rates reported by Vowles et al, other reviews reported rates of misuse varying from 8% to 16%, of abuse ranging from 0.43% to 8%, and of addiction ranging from 0.05% to 14% (*Voon et al. Subst Abuse Treat Prev Policy 2017*). An earlier systematic review by Minozzi et al. that used the DSM IV or ICD-10 definition of "opioid dependence syndrome" reported a median incidence of 0.5% (range 0-24%) and a median prevalence rate of 4.5% (range 0-31%) (*Minozzi et al. Addiction 2012*). These studies underscore the difficulty in measuring addiction in heterogeneous populations.

One recent review found that, "Rates of carefully diagnosed addiction have averaged less than 8% in published studies" (*Volkow & McClellan N Eng J Med 2016*). It added: "addiction is not a predictable result of opioid prescribing. Addiction occurs in only a small percentage of person who are exposed to opioids—even among those with preexisting vulnerabilities." Hence, although each of these studies has limitations, it was not and is not unreasonable to refer to the risk of addiction as low, or as infrequently occurring, and such statements would not have been misleading to reasonable physicians and others. As the FDA has stated on a webpage published in 2009 and last updated in December 2018: "According to the National Institutes of Health, studies have shown that properly managed medical use of opioid analgesic compounds (taken exactly as prescribed) is safe, can manage pain effectively, and rarely causes addiction" (FDA webpage, Exhibit 21 to Lembke deposition).

Although there is a well-known association between higher doses of opioids and opioid use disorder, it is important to note that this is a correlation and does not indicate a 'cause-and-

effect' relationship, nor does it imply that there is a specific dose threshold that should not be exceeded (*Coyle et al. Pharmacoepidemiol Drug Saf 2018*). According to a report by the National Academies of Sciences, Engineering and Medicine (NASEM), "It is important to acknowledge that an overwhelming majority of people who use prescription opioids do not continue to use them chronically, and so are not at risk of switching to heroin." (*National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse; Phillips JK, Ford MA, Bonnie RJ, editors, Washington (DC): National Academies Press, 2017; Shah et al. MMWR 2017*).

I. PSEUDOADDICTION IS A LEGITIMATE CONCEPT

I disagree with the view of plaintiffs' and their experts that Janssen inappropriately promoted the concept of "pseudoaddiction." The term pseudoaddiction originated in 1989 from a single case report describing a 17-year-old boy with acute leukemia and chest wall pain from pneumonia (*Weissman and Haddox. Pain 1989*). Since that time, over 200 articles have been written on it. Generally, speaking, the term refers to a person who exhibits drug-seeking and other behaviors suggesting addiction because their pain is not being adequately treated (i.e. iatrogenic harm was caused by withholding treatment, rather than providing it). It has since fallen under scrutiny, with several publications questioning its validity (*Greene and Chambers. Curr Addict Rep 2015*). Recent articles have contended that both pseudoaddiction and addiction are best understood as social rather than biological constructs, such that the diagnosis says more about society and the clinician than the patient (*Bell and Salmon. Int J Drug Policy 2009*).

Regardless of whether one uses the term, the theory that suboptimal pain control may result in drug-seeking behavior is well-supported and was not invented by the pharmaceutical industry. The concept dates back to at least the early 1970's when Marks and Sachar published a study in the official journal of the American College of Physicians suggesting that "misconceptions [by physicians] probably lead to undertreatment with narcotic analgesics, causing much needless suffering in medical inpatients" (*Marks and Sachar. Ann Intern Med 1973*). Similarly, the concept of pseudoaddiction is reflected in FDA-approved labeling of opioid medications to this day. For example, the September 2018 Duragesic label approved by the FDA states, "Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control" (page 34, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/019813s075s076lbl.pdf (last accessed April 24, 2019).

This phenomenon is more pronounced in conditions with subjective outcomes such as pain and psychiatric illnesses. Given the very wide variability in dosing for opioids (i.e. some patients may require much higher doses to respond than other patients due to differences in genetics, metabolism, age, concomitant medications and co-existing conditions), the international emphasis on the treatment of pain (e.g. poorly treated acute pain predisposes people to chronic pain (*Badiola IJ. Anesthesiol Clin 2016*) and patient-centered online forums where under-treatment is discussed among patients), there were almost certainly patients who exhibited behaviors that could be consistent with both true addiction and under-treatment of pain in a

person prescribed a sub-therapeutic dose. According to a recent survey by the Substance Abuse and Mental Health Services Administration, over 60% of patients who abuse opioids do so to alleviate physical pain (*SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health (NSDUH), 2015*). I have seen this in my own practice. It is therefore the physician's responsibility to consider and adequately assess the patient for both possibilities.

IX. JANSSEN OPIOID MEDICATIONS

A. DEVELOPMENT OF DURAGESIC

In light of the growing recognition in the medical community of the burden of chronic pain and its long-term sequelae, the federal government began efforts to improve pain treatment, including the development and more aggressive use of opioid medications. In 1977, the Dept. of Health and Human Services' Interagency Committee on New Therapies for Pain and Discomfort was created at the request of the White House. In 1981, this committee, whose members included scientists and physicians, concluded that new opioid medications and delivery systems were needed to address untreated pain. This committee sent a letter to the pharmaceutical industry asking manufacturers to create such new medications (*Rationale for the Development, Therapeutic Use, and Clinical Program for Transdermal System (Fentanyl), JAN-MS-02908137*). The scientific study of heroin and approval of Dilaudid-HP were 2 of the consequences of this request. In response to this solicitation, ALZA submitted a proposal on June 16, 1982 to the FDA, c/o Drs. Edward Tocus and Marion Finkel, with the IND being filed in June 1984. Duragesic was subsequently developed by ALZA.

The Duragesic NDA included 17 short-term and 3 long-term trials on safety and efficacy. For the short-term studies, a total of 376 patients participated; 238 received varying doses of TTS-fentanyl (50, 75, 100 mcg/hr), and 138 received placebo (JAN-MS-00213627 at 1.1/214). Respiratory depression occurred in 14 of the 238 patients (Id. at 1.1/224-232). Investigators ultimately concluded that "TTS (fentanyl) is safe and well-tolerated when used alone or when supplemented with other narcotics" (Id. at 1.1/236). For the long-term studies, id. at 1.1/270, of the 72 patients who were treated with Duragesic, 24 patients wore the Patch between 61-90 days, 20 wore it for between 91-120 days, and 16 wore it for more than 120 days (5 of whom continued for more than a year) (Id. at 1.1/277). Investigators ultimately "conclude[d] from these studies that long-term administration of [the fentanyl Patch] [wa]s a safe and acceptable analgesic therapy for patients with advanced cancer" (Id. at 1.1/294).

B. DEVELOPMENT OF NUCYNTA AND NUCYNTA ER

After the release and clinical studies showing the efficacy and lower abuse potential of the mixed-mechanism opioid, tramadol, tapentadol was developed by Gruenenthal GmbH in Germany, representing an entire new class of medications. Unlike tramadol, which is a partial mu agonist, tapentadol is a full mu agonist with a binding affinity 20-50 x less than morphine, and is therefore 2 to 3 times more potent than tramadol. In addition to its mu agonist properties, animal studies have shown that tapentadol inhibits the reuptake of norepinephrine, which is a

neurotransmitter involved in the chronic pain. Pivotal trials performed in the 2000's established efficacy for acute postoperative pain, low back pain, knee and hip osteoarthritis, and diabetic neuropathic, making tapentadol the first opioid to receive FDA approval for neuropathic pain (*Stegmann et al. Curr Med Res Opin 2008; Kleinert et al. Anesth Analg 2008; Hale et al. Curr Med Res Opin 2009; Hartrick et al. Clin Ther 2009; Schwartz et al. Curr Med Res Opin 2011*).

The Nucynta IR NDA lists two "pivotal" Phase III studies supporting the efficacy of tapentadol IR in the treatment of moderate to severe pain, id. at 19, and one long-term 90-day efficacy study (JAN-MS-00230459 at 40). With respect to safety, the NDA submission focused on three pooled safety analysis sets for the 9 phase 2/3 clinical studies (Id. at 45). Overall, a total of 1880 subjects received multiple-doses of tapentadol IR (21 mg to 120 mg) in the 7 Phase 2/3 multiple-dose double-blind studies. These included 449 subjects with moderate to severe pain who received tapentadol IR for at least 45 days, with 318 of these subjects receiving tapentadol IR (50 mg or 100 mg every 4 to 6 hours, as needed) for at least 90 days in the 90-day safety study, KF5503/34 (Id. at 46). The authors concluded that "Overall, tapentadol IR (50 mg to 100 mg) provides analgesia similar to the classical mu-opioid analgesic oxycodone IR..." and that "Tapentadol, with its dual mechanism of action, demonstrates improved gastrointestinal tolerability (specifically in the incidence of nausea and/or vomiting [composite measure] and constipation) compared to oxycodone at doses providing similar pain relief" (Id. at 74).

Janssen received FDA approval for Nucynta in immediate-release form in 2008, which was launched in 2009 for an indication of "moderate-to-severe acute pain in patients 18 years of age and older". In 2011, an extended-release form was approved for "moderate-to-severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time". The following year, the ER indication was expanded to included diabetic peripheral neuropathy.

The initial Nucynta ER NDA in 2009 involved 10 Phase II and III trials conducted to examine the efficacy of tapentadol ER (JAN-MS-00214445 at 22). With respect to safety, the data submitted to the FDA included safety data from 38 completed clinical studies with the tapentadol ER formulation (28 Phase 1, 4 Phase 2 double-blind studies, 5 Phase 3 double-blind studies, and 1 Phase 3 open-label study), and 2 tapentadol IR Phase 3 studies (PAI-3016/KF35 and PAI-3018/KF38) that were completed post-Nucynta IR NDA (which also included studies whereby patients were exposed to the ER formulation (Id. at 46). The DPN indication was approved with the first supplement to the NDA (S-001) based on two studies. Data from two randomized-withdrawal, placebo-controlled phase 3 trials showed, among patients who had at least a one-point reduction in pain intensity during three weeks of treatment with NUCYNTA® ER, those who continued on the same dose of NUCYNTA® ER that was titrated to balance individual tolerability and efficacy (100-250mg twice daily) for an additional 12 weeks experienced significantly better pain control compared to those who switched to placebo (Id. at 32).

Compared to other ER opioids, Nucynta ER has a more favorable safety and abuse profile, and comes in a tamper-resistant formulation (*Butler et al. Pain Med 2015; Dart et al. Pain Med 2016; Cepeda et al. J Pain 2013; Galia et al. J Opioid Manag 2014; Wild et al. Pain*

Practice 2010). Studies have shown efficacy comparable or superior to oxycodone in multiple patient populations, with less adverse effects (*Daniels et al. Curr Med Res Opin 2009; Lange et al. Curr Med Res Opin 2017; Serrie et al. Curr Med Res Opin 2017*). Because it is a dual mechanism opioid, it has a lower incidence of gastrointestinal side effects than pure mu agonist opioids, and may be associated with the slower development of tolerance and less euphoria (*Vadivelu et al. Anesthesiology Clin 2017; Caputi et al. Minerva Med 2019*).

C. REASONS FOR PRESCRIBING DURAGESIC, NUCYNTA, AND NUCYNTA ER

Since the efficacy of different opioids is similar, other reasons form the cornerstone for prescribing decisions including pain characteristics, side effect profile, personal experience, marketing, interpretation of the available data, preauthorization issues, insurance and formulary decisions, pricing (e.g. co-pays), patient preference and co-morbidities, and community standards. In particular, due to insurer policies and practices, many patients have limited access to other pain treatments, such as physical therapy and non-opioid medicines (*Biotechnology Innovation Organization, Toolkit, available at: https://www.bio.org/sites/default/files/docs/toolkit/IGP15.pdf*). This is true for both government programs like Medicare and Medicaid, as well as in the commercial sector. As to the role of promotion by pharmaceutical companies, in my experience there is a diminishing effect of promotion as time goes on. One reason for this is that additional information sources become available over time, such as publications in medical literature and clinicians' experience with the medication. Another reason is that new medications become available.

1. Duragesic

Duragesic is somewhat unique among extended-release schedule II opioids, and at one point comprised a plurality of my patients on chronic opioid therapy with chronic, constant pain. Whereas individuals with purely incident pain may derive the best benefit from short-acting opioids, those with constant pain (which is estimated to occur in 67% of individuals with chronic pain; *Kennedy et al. J Pain 2014*) should theoretically benefit most from a medication with pharmacokinetics that match their pain pattern. In medicine, peak blood levels are generally associated with toxicity and for opioids, greater euphoria (e.g. injecting heroin causes a profound euphoria because it is ultra-short acting), while trough levels more closely reflect therapeutic levels (*Kang and Lee. Korean J Intern Med 2009*). The conceptual appeal of Duragesic is that it affords better steady-state blood levels than nearly any other opioid compound, can result in uninterrupted sleep when pain interferes with sleep, and has a lower rate of abuse and diversion than other 'strong' opioids. Because there are local opioid receptors in the gastrointestinal tract, the incidence of constipation and possibly nausea and vomiting are less with transdermal delivery (*Staats et al. South Med J 2004; Ackerman et al. Consult Pharm 2004; Allan et al. BMJ 2001; Allan et al. Spine (Phila PA 1976) 2005; Donner et al. Pain 1996; Wang et al. J Cancer Res Ther 2018*). For individuals who have trouble swallowing pills, or who are nihil per os for medical reasons (e.g. pancreatitis, inflammatory bowel disease exacerbation), transdermal delivery systems may provide the best, or only, means for non-parenteral administration. Compliance may also be better with transdermal formulations, especially in individuals with

cognitive issues (*Singh and Morris. Int J Pharm Investig 2011*). Multiple randomized studies have also demonstrated superior quality of life and satisfaction for chronic pain than other sustained-release formulations (*Allan et al. BMJ 2001; Allan et al. Spine (Phila PA 1976) 2005; Donner et al. Pain 1996; Wang et al. J Cancer Res Ther 2018*). Still other studies have demonstrated better pain relief and quality of life in individuals who were switched from oral opioid formulations to transdermal fentanyl (*Zernikow et al. J Pain 2007; Ikeda et al. Gan To Kagaku Ryoho 2012*). In a book chapter authored by Dr. Schumacher and colleagues, when discussing alternative routes of administration on page 523 the authors wrote, "Another example is the transdermal patch for systemic effects that provide stable blood levels of a drug and better pain control while avoiding the need for repeated parenteral injections. Fentanyl has been the most successful opioid in transdermal application and finds use in pain relief for patients experiencing chronic pain" (*Way WL, Fields HL, Schumacher MA. Opioid analgesics and antagonists. In: Katzung BG. Basic and Clinical Pharmacology. Lange/ McGraw-Hill, NY, 512-31.*).

2. Nucynta and Nucynta ER

Nucynta is likewise unique among schedule II opioids in that it may be better suited to alleviate neuropathic pain via its ability to inhibit the reuptake of norepinephrine (similar to venlafaxine, greater than tramadol). Its ability to inhibit serotonin reuptake is very weak, and contributes very little to its analgesic effects. Compared to morphine, its affinity for the mu receptor is about 20-50 times less; it also has lower affinity for the kappa and delta opioid receptors, though the relative difference is less. However, because of its other properties, it is only about 2 to 3 times less potent than morphine. Nucynta has shown efficacy in nociceptive (somatic and visceral pain), cancer pain and neuropathic pain (*Zajaczkowska et al. Pharmacol Rep 2018*).

The other opioid with a ceiling effect and lower abuse potential than conventional opioids is tramadol, which is a schedule III opioid that inhibits the reuptake of both norepinephrine and serotonin. Compared to tramadol, tapentadol is 2-3 times as potent. However, tapentadol holds several other advantages over tramadol besides a possibly higher ceiling effect including a lack of requirement for metabolic activation, minimal serotonergic effects (including risk for serotonin syndrome), more linear pharmacokinetics, greater gastrointestinal tolerability, and possibly a lower risk of abuse (i.e. shorter duration of euphoria) (*Faria et al. Eur J Pain 2018; Stoops et al. Psychopharmacology 2013*).

Nucynta comes in immediate and once per day extended release formulations, which makes it useful for both constant, chronic pain, and incident or breakthrough pain. Because of its lower affinity for opioid receptors, it has a more favorable side effect profile than traditional mu agonists regarding gastrointestinal, cognitive and other adverse effects. Tapentadol has been shown to have no adverse effects on cardiovascular function (e.g. changes in blood pressure or prolonged QT interval), and minimal effects on hormone dysregulation (e.g. osteoporosis, impaired fertility and sex drive, depression) (*Coluzzi et al. J Pain Res 2015; Biondi et al. J Pain 2011; Eichenbaum et al. J Opioid Manag 2015; Coluzzi et al. Ther Clin Risk Manag 2015*).

D. DURAGESIC, NUCYNTA, AND NUCYNTA ER HAVE FAVORABLE ABUSE PROFILES

In one study that sought to validate a new instrument for opioid abuse potential, the Duragesic reservoir patch had the lowest abuse potential among 14 opioid agonists evaluated (the Matrix patch ranked 11th out of 14, behind Stadol nasal spray (both were behind Suboxone, which is a mixture of buprenorphine and naloxone approved for the treatment of opioid addiction; *Butler et al. Harm Reduct J 2006*). For adverse events, most are comparable to placebo, and because it reaches the bloodstream via transdermal applications, the incidence of gastrointestinal side effects, which are the most common and a principal reason for discontinuation, is less than for medications given orally that transit the gut (*Rausch and Jansen. US Pharm 2012; Boswell et al. J Opioid Manag 2010; Swedish Council on Health Technology Assessment, 2006*). The more recent advent of the matrix patch has improved tolerance of transdermal fentanyl (skin compatibility, comfort, adhesive properties, satisfaction), and possibly reduced abuse potential and risk of accidental overdose (*Freynhagen et al. J Pain Symptom Manage 2005; Margett and Sawyer. Continuing Education in Anaesthesia Critical Care & Pain 2007*).

Compared to other opioids, tolerance develops slower to tapentadol (*Tzschenke et al. Drugs Today 2009; Hartrick and Rozek. CNS Drugs 2011*) and the risk of addiction and diversion have been shown in multiple studies to be significantly lower (*Butler et al. Pain Med 2015; Dart et al. Pain Med 2016; Cepeda et al. J Pain 2013*). Nevertheless, abuse deterrent formulations are available (*Galia et al. J Opioid Manag 2014*).

For the reasons above, I disagree with plaintiffs' expert Dr. Kessler that any of the materials he cites support the conclusion that Janssen misled physicians or others regarding the benefits or risks of Duragesic, Nucynta, or Nucynta ER.

X. ADDITIONAL STATEMENTS ATTRIBUTED TO JANSSEN BY PLAINTIFFS AND THEIR EXPERTS WERE NOT MISLEADING

In the discussion above, I have indicated my disagreement with several opinions advanced by plaintiffs' experts. I expand on my opinions on related issues here.

A. EFFECTIVENESS FOR NON-CANCER PAIN

In my opinion the statements that plaintiffs and their experts attribute to Janssen were not deceptive, fraudulent or misleading, and need to be viewed in the context of the extant information and prevailing views in the medical community at the time. As noted above in numerous locations, opioids have been shown to be effective in well-designed placebo-controlled trials for up to 12 weeks for non-cancer pain, and in open-label studies for much longer follow-up periods. Neither non-opioid analgesics for non-cancer pain, nor opioid or non-opioid analgesics for cancer pain, been studied in placebo-controlled trials for more than 12 weeks because of FDA requirements, practical issues (i.e. institutional review board approval) and ethical concerns. In a highly-cited systematic review from 2007, Finnerup et al. found that

opioids were not only more effective than gabapentinoids, serotonin-norepinephrine reuptake inhibitors, topical lidocaine and N-Methyl-D-Aspartate receptor antagonists (they were equally efficacious as tricyclic antidepressants), but that the number-needed-to-harm (a measure of toxicity) was actually higher for opioids (indicating they are associated with less serious side effects) than for tricyclic antidepressants and SNRIs, NMDA antagonists, pregabalin, and topiramate (*Finnerup et al. MedGenMed 2007*).

B. OPIOIDS IN THE TREATMENT ALGORITHM

Most algorithmic treatment guidelines have been developed for neuropathic pain, and so it is important to note that: 1) neuropathic pain accounts for only about 15%-25% of cases of chronic pain (*Torrance et al. J Pain 2006; Bouhassira et al. Pain 2008*); and 2) neuropathic pain has been shown to be more resistant to opioid treatment than non-neuropathic pain (*Arner and Myerson. Pain 1988; Portenoy et al. Pain 1990*).

In an earlier review by Finnerup and colleagues that evaluated over 100 clinical trials involving more than a dozen medications, opioids were found to be the most efficacious medication among medications that contained sufficient data, and the authors recommended them as 2nd or 3rd line treatments for neuropathic pain (*Finnerup et al. Pain 2005*). The European Federation for Neurological Sciences recommended strong opioids as a 2nd line treatment for postherpetic neuralgia and central neuropathic pain (*Attal et al. Eur J Neurol 2010*), the Canadian Pain Society recommended them as a 2nd line treatment for all neuropathic pain (*Moulin et al. Pain Res Manag 2014*), and the IASP Neuropathic Pain Special Interest Group recommended strong opioids as a 2nd line treatment, though in certain circumstances such as the treatment of acute neuropathic pain, neuropathic pain due to cancer, episodic exacerbations of severe neuropathic pain, and when titrating another medication to effect, they could be considered as 1st line (*Dworkin et al. Pain 2007; Dworkin et al. Mayo Clin Proceed 2010*). A randomized trial by Keskinbora and colleagues performed in patients with neuropathic cancer pain found morphine in conjunction with gabapentin to be superior to opioid monotherapy, and recommended the combination as a 1st line treatment (*Keskinbora et al. J Pain Symptom Manage 2007*).

C. QUALITY OF LIFE

As noted above, opioids have been shown in meta-analyses and numerous studies and surveys to improve quality of life (*Thornton et al. Qual Life Res 2017; Goesling et al. 2019; Allan et al. BMJ 2001; DiJulio et al. Washington Post 2016*). In one earlier review, Devulder et al. found that 3 of 4 randomized trials, and 4 out of 5 observational studies found that opioids improved quality of life, including some studies that followed patients for over one year (*Devulder et al. Curr Med Res Opin 2005*).

D. PSEUDOADDICTION

As noted previously in the report, the concept of pseudoaddiction was introduced years before Dr. Haddox coined the term in 1989 (*Weissman and Haddox. Pain 1989; Marks and Sachar. Ann Intern Med 1973*). The validity of the concept has been noted by the FDA in its

literature (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/019813s075s076lbl.pdf), and has been affirmed in psychiatry literature (*Griffith LJ. Psychiatry (Edgmont) 2008; Bates B. Watch for the Hallmarks Of 'Pseudoaddiction' Clinical Psychiatry News, Sept 1, 2005. Available at: https://www.mdedge.com/psychiatry/article/22399/addiction-medicine/watch-hallmarks-pseudoaddiction*). In a clinical setting, the relevance of this concept is that patient behavior that appears to focus on securing additional pain medication is not necessarily evidence of addiction or a substance-use disorder (i.e. there are many cases where physicians under-appreciate and undertreat chronic pain, particularly in vulnerable populations) (*Campbell and Edwards. Pain Manag 2012; Hoffman et al. Proc Natl Acad Sci 2016; Birnie et al. Pain Res Manag 2014; Kaye et al. Ochsner J 2010; Griffioen et al. Curr Alzheimer Res 2017*). Assessing whether additional pain treatment, including but not limited to opioids, is appropriate for such a patient requires an individualized and comprehensive examination by qualified medical professionals. Some pain patients who appear to be seeking opioid medicines for an improper purpose are in fact, upon closer examination, simply trying to find adequate relief for their pain while taking opioid pain medicines as prescribed. I, and countless other pain practitioners, have witnessed this phenomenon numerous times in clinical practice.

XI. OTHER ASSERTIONS BY PLAINTIFFS' AND THEIR EXPERTS ARE UNFOUNDED AND UNPERSUASIVE.

I have also identified below additional disagreements I have with plaintiffs' experts and witnesses in this matter not addressed elsewhere.

A. DR. MARK SCHUMACHER

Schumacher report page 6, # 8: Dr. Schumacher asserts that in the field of pain medicine, the standard of care (SOC) was changed as a result of widespread promotion and marketing of opioids by the Defendants. I disagree with Dr. Schumacher. First, Dr. Schumacher misunderstands the term 'standard of care', which come from a high, usually unchallenged authority, and dictate mandatory, widely-accepted practices that support formal policies. Guideline are recommendations to users when specific standards do not apply. They are meant to be more flexible, should be open to interpretation and do not need to be followed to the letter. There are no 'standards' on the treatment of chronic pain, and guidelines differ based on condition (i.e. they are different for back pain, neuropathic pain, fibromyalgia) and sponsor. For example, for knee osteoarthritis, both the American Academy of Orthopedic Surgeons and the American College of Rheumatology recommend tramadol (AAOS found the evidence for strong opioids to be inconclusive while ACR (for hip, knee and hand) recommended stronger opioids in patients who did not want or could not undergo joint replacement) (*Hochberg et al. Arthritis Care Res (Hoboken) 2012; Jevsevar DS. Treatment of osteoarthritis of the knee: evidence-based guideline, 2nd edition. Am Acad Orthop Surg 2013*). The United Kingdom's National Institute for Health and Care Excellence (NICE) recommends strong opioids for knee OA, especially in the elderly (*The National Clinical Guideline Centre (UK). Osteoarthritis: Care and management in adults. London: National Institute for Health and Care Excellence (UK); 2014 Feb.*). In 2007, the International Association for the Study of Pain (IASP) recommended tramadol and strong

opioids as 2nd line treatments for neuropathic pain (*Finnerup et al. MedGenMed 2007*). In 2015, the use of strong opioids was changed to a 3rd line treatment, while tramadol remained 2nd line (*Finnerup et al. Lancet Neurol 2015*).

Second, Dr. Schumacher errs in attributing increases in opioid prescribing to promotion by industry. Industry-sponsored lectures are not eligible for continuing medical education credits, and multiple articles written by experts who did not receive industry funding advocated their use for chronic pain (*Ballantyne and Mao. N Engl J Med 2003*). At all times, literature has acknowledged the risks of opioid medicines. For example, in a book chapter written by Dr. Schumacher and colleagues, they note, "Use of opioid drugs in acute situations may be contrasted to their use in chronic pain management, where other factors must be considered-particularly tolerance and physical dependence." They then go on to mention several other factors that should be considered in the decision, including drug-drug interactions and co-morbidities, among others. Since tolerance and physical dependence do not occur in patients who are not taking opioids, this implies that they may be a reasonable choice. At the end of the same paragraph on page 522, the authors state, "The most common error made by physicians in using opioid analgesics is failure to provide a sufficient dose to achieve optimal relief. Patients vary widely in their response, so dosing must be individualized for each." On page 525, the authors go on to note (in italicized print), "Obviously, the risk of causing dependence is an important consideration in the therapeutic use of these drugs (opioids). Despite that risk, under no circumstances should adequate pain relief ever be withheld simply because an opioid exhibits potential for abuse or because legislative controls complicate the process of prescribing narcotics (*Way WL, Fields HL, Schumacher MA. Opioid analgesics and antagonists. In: Katzung BG. Basic and Clinical Pharmacology. Lange/ McGraw-Hill, NY, 512-31*).

Schumacher report page 6, # 10: Dr. Schumaker asserts that in the field of pain medicine, for the vast majority of patients, the risks of prescription opioids outweigh any benefits, and that only a small percentage of chronic pain patients achieve meaningful relief. I disagree with Dr. Schumacher. This is the opinion of one practitioner who did not complete a pain fellowship. To generalize one's own experience with a particular patient population to that of others is antithetic to personalized medicine and evidence-based practice. For example, one cannot assert that epidural steroids are ineffective in all people because most patients with mechanical low back pain do not benefit. Personalized medicine entails tailoring treatment to an individual patients' clinical condition, taking into account their preferences and likelihood of benefit. For some individuals, the risks of chronic opioid therapy (COT) may indeed outweigh the benefits, but for others (e.g. an elderly person with multiple co-morbidities who has failed conservative therapy and is facing a choice of opioids prescribed in a controlled environment or surgery), the benefits outweigh the risks.

B. DR. ANNA LEMBKE

Lembke report page 21, # 4: Dr. Lembke asserts "The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including overstatement of benefits of long-term use for chronic pain. In fact, there is not, and has never been, reliable evidence that long-term opioid use improves pain or function to any clinically

meaningful degree. The best evidence available suggests that there is little or no improvement in pain or function for most patients on long-term opioid therapy." I disagree with Dr. Lembke.

This statement is provably false and an oversimplification. A recent systematic review by Thornton et al. on health-related quality of life in patients receiving long-term opioid therapy found statistically significant benefits for improved physical functioning (*Thornton et al. Qual Life Res 2017*). This was confirmed in a recent survey by the Washington Post and Kaiser Foundation, which found that 57% of long-term opioid users reported improvements in quality of life vs. 16% who reported that their quality of life has deteriorated (*DiJulio B et al. 2016. Available at: https://www.kff.org/report-section/the-washington-post-kaiser-family-foundation-survey-of-long-term-prescription-painkiller-users-and-their-household-members-executive-summary/*). Even in studies that have been cited for the idea that opioid therapy has limited benefits such as the recent SPACE study published in JAMA comparing opioids to non-opioid pharmacotherapy for knee or hip osteoarthritis, a close examination of the data supports opioids in some contexts (*Krebs et al. JAMA 2018*). In the non-opioid arm, tramadol was permitted, but tramadol is a controlled substance and binds to opioid receptors, and has been described to be analgesically equivalent to codeine with a similar side effect profile to other opioids (*Manchikanti et al. Pain Physician March/April 2019*). FDA classifies tramadol as an opioid; Ultram, a product containing tramadol, contains black-box warnings regarding "the risks of opioid addiction, abuse and misuse," and is part of the FDA REMS program (Ultram Medication Guide 2017, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020281s042s043lbl.pdf). For the primary outcome measure of functional improvement, no differences were found between groups. However, 59.0% of patients allocated to opioids experienced meaningful improvement vs. 60.7% in the non-opioid group. In this study, which was characterized by high surveillance and rigorous screening, there were no significant differences between groups for adverse events or prescription misuse. An even more recent study performed in 49 individuals who wanted to taper off opioids found that significantly more people experienced worsening pain and function than who improved after cessation (*Goesling et al. Pain 2019*). As was noted in the Dept. of Health and Human Services report on pain management best practices, the absence of robust data on the duration of opioid effectiveness should not be misinterpreted as a lack of effectiveness (*U.S. Dept. of Health and Human Services Pain Management Best Practices Inter-Agency Task Force. Draft Report on Pain Management Best Practices: Updates, Gaps, Inconsistencies, and Recommendations. Available at: https://www.hhs.gov/ash/advisory-committees/pain/reports/2018-12-draft-report-on-updates-ga*). At best, this data support the typical practice of starting a chronic pain patient on non-opioid therapy and considering opioids if non-opioid therapy fails.

Moreover, Dr. Lembke erroneously imputes scientific knowledge gain in the last several years to the state of science more than a decade ago. The position that opioids do not improve function was clearly a minority one in the early 2000's. In a commissioned review by Drs. Jane Ballantyne and Jianren Mao in the New England Journal of Medicine, the authors wrote, "… Despite this recommendation, many physicians remain uncertain about prescribing opioids to treat chronic pain and do not prescribe them. Some physicians argue that opioids are only

marginally useful in the treatment of chronic pain, have a minimal effect on functioning, and may even worsen the outcome. However, this seems to be a minority view. Key organizations (Federation of State Medical Boards, American Pain Society and American Academy of Pain Medicine) that strongly support the use of opioids to treat chronic pain have published consensus statements to guide physicians in prescribing these drugs (*Ballantyne and Mao. N Engl J Med 2003*)."

On page 37 of her report, Dr. Lembke asserts "The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including making inaccurate understatements of the risks of addiction to opioids. Even when being prescribed by a doctor for a legitimate pain condition, opioid painkillers are as addictive as heroin purchased on a street corner, because the prescription opioids have the same addictive effects on the neurocircuitry of the brain. There is not, and has never been, scientific support for the claim that the risk of addiction from chronic opioid therapy is low, "rare," or "less than 1%." In fact, the best evidence available shows that the risk of addiction in patients taking opioids for chronic pain is between 10% and 40%. In teens and young adults, the evidence shows that even very limited exposure to prescription opioids can result in addiction. So-called "abuse-deterrent formulations" do not lower the risk of addiction among patients taking them as prescribed." I disagree with Dr. Lembke.

The reported prevalence of any condition is inextricably related to the population studied, how the condition is defined, and the methods of surveillance. For example, in a study involving elderly people with back pain radiating down to their lower legs, the prevalence of spinal stenosis would be dramatically higher than in an active duty population with back pain. These differences can account for the wide range of reported rates of addiction in the literature varies widely, which range from less than 1% to over 50%. In the aforementioned systematic review published in 'Pain', Vowles and colleagues found estimates of misuse ranging from 21% to 29%, and that of addiction from 8% to 12% (*Vowles et al. Pain 2015*).

Part of the issue with 'addiction' is that it is not a 'disease' (despite what is often written in the lay literature) with defined pathognomonic mechanisms and objective diagnostic criteria (*Holden T. CMAJ 2012*). In fact, there is no disorder called "opioid addiction" in DSM V; the term is more appropriately called "opioid use disorder". In individuals who are indiscriminately prescribed opioids, the incidence of abuse will increase; however, the decision to prescribe an opioid, or any medication for that matter, is up to the physician, and must take into account the anticipated risks and benefits. Randomized studies almost always have more stringent selection criteria than uncontrolled studies, and an examination of reported addiction rates in these studies (from a systematic review and meta-analysis published by Thornton et al. published in Qual Life Res in 2017 yields a very different picture. Among the 4 studies that followed patients for at least 16 weeks and reported adverse events, there were no reported cases of addiction in 1470 participants (*Binsfield et al. Pain Pract 2010; Kalso et al. BMC Med 2007; Nicholson et al. CUrr Med Res Opin 2006; Rauck et al. J Opioid Manag 2007*).

Regarding the comment on abuse-deterrent formulation, Dr. Lemke's interpretation of the extant data is in contrast with the literature. Numerous studies have shown lower abuse potential

(and abuse is a precursor and component of addiction) for abuse-deterrent opioids (*Kopecky et al. J Clin Pharmacol 2017; Lamb et al. Drugs 2016; Bannwarth B. Drugs 2012*), and in the event of abuse, which is technically more difficult for most compounds, formulations that embed opioid antagonists (e.g. Embeda) have a built-in safety mechanism that can prevent overdose. It is important to recognize that these medications were approved by the FDA.

On page 63 of her report, Dr. Lembke states, "The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including making inaccurate claims as to the levels to which doses can be safely increased. With increasing dosage and duration of opioids, the risk of addiction goes up, as do the risks of many other adverse health consequences, including tolerance, dependence, withdrawal, opioid induced hyperalgesia, immunosuppression, severe constipation, depression, cognitive decline, cardiac effects, breathing effects, hormonal effects, accidental overdose, and death. There is an undeniable link between suicide and opioids. Opioids are associated with more adverse medical outcomes and more mortality than non-opioid analgesics (NSAIDS)." I disagree with Dr. Lembke.

As noted above, the issue of a "ceiling effect", or lack thereof, was not invented by the pharmaceutical industry. Opioids can be used to induce general anesthesia, and the assertion that pure mu agonists lack a ceiling effect has previously been used by anesthesiologists, who comprise a plurality of interventional pain physicians, by pharmacologists, and in government documents (*Trescot et al. Pain Physician 2008; Bovill JG. Drugs 1987; Jaffe and Martin. The Pharmacological Basis of Therapeutics.*). The common saying that there is no 'set limit' as to how high opioids can be escalated stems from several factors:

1. The FDA did not put specific dosing limits on labels for chronic pain and studies have used very wide ranges.
2. Tolerance, which refers to a reduced physiological effect to a medication with repeated use, develops to opioids. Unlike opioid-induced hyperalgesia, tolerance should not be used as grounds to reduce opioid dose, as tolerant individuals generally respond with pain relief to dose escalation (*Chen et al. J Opioid Manag 2014*).
3. Tolerance develops to opioids more rapidly than to other medications, and there are several causes of tolerance including receptor desensitization, internalization and down-regulation, uncoupling of the link between opioid receptors and G proteins, enhanced metabolism and behavioral tolerance.
4. There are multiple factors that reduce opioid responsiveness such that individual differences can vary dramatically. These include male gender, younger age, negative affect, genetics, lower temporal summation, high endogenous levels of opioids (e.g. fibromyalgia), higher weight and volume of distribution, and medications (*Bruehl et al. J Pain 2013*).

As such, the concept that pure mu agonists "lack of a ceiling effect" predated the use of sustained-release opioids, and largely refers to the fact that in patients receiving opioids for chronic pain, there are very large differences in the therapeutic dose range. In a 2003 New England Journal of Medicine article cited more than 1000 times, Jane Ballantyne and Jianren Mao acknowledge the earlier widespread belief that opioids had no ceiling effect, and that there

was no clear-cut dose limit, by stating, "The concept of a ceiling dose of opioids in the treatment of chronic pain is growing, yet it is difficult to define a dose that could be recommended as a ceiling. Daily doses above 180 mg of morphine or a morphine equivalent have not been validated in clinical trials involving patients with chronic pain and might be considered excessive (*Ballantyne and Mao. N Engl J Med 2003*)." Although the authors state that doses above 180 mg have not been studied in high quality clinical trials (much higher doses have been studied and reported effective; *Kahan et al. Can Fam Physician 2006; Nugent et al. J Pain Symptom Manage 2001 (Duragesic*)). In fact, the polyanalgesic consensus guidelines on intrathecal drug therapy recommend morphine in patients who obtain significant analgesia but have intolerable side effects, and almost every patient on intrathecal opioids is receiving an oral morphine equivalent dose exceeding 200 mg (morphine is FDA-approved, with the indication for Duramorph being "For the management of pain severe enough to require use of an opioid analgesic by intravenous administration and for which alternative treatments are not expected to be adequate (*Deer et al. Neuromodulation 2017*)."

Regarding the statement that the risks of opioid therapy exceed that of NSAIDs, it depends on the population. In individuals at high risk from NSAIDs (whose risks include gastritis and ulcers, stomach perforation, renal failure gastrointestinal bleeding, hemorrhage, stroke and heart attack), the risks of NSAIDs may exceed opioids, and there are many patients for whom NSAIDs are contraindicated (opioids are not contraindicated in specific patient populations, but rather should be used cautiously in high-risk individuals). The risk of NSAID therapy increases dramatically in the elderly (*Marcum and Hanlon. Ann Longterm Care 2010*).

C. DR. DAVID KESSLER

On pages 536-7 of his deposition, Dr. Kessler asserts that FDA label for Duragesic was never meant to be for chronic, non-cancer pain. I disagree with Dr. Kessler.

This is false, and in fact the FDA has refuted this (Docket No. FDA-2012-P-0818). In response to PROP's request to change to the label of extended release/ long-acting opioids for non-cancer pain, the organization wrote, "It is the FDA's view that a patient without cancer, like a patient with cancer, may suffer from chronic pain, and PROP has not provided any scientific support for why labeling should recommend different treatment for such patients. In addition, FDA knows of no physiological or pharmacological basis upon which to differentiate the treatment of chronic pain in a cancer setting or patient from the treatment of chronic pain in the absence of cancer… FDA therefore declines to make a distinction between cancer and non-cancer chronic pain in opioid labeling." The lack of a pathophysiological distinction between cancer and non-cancer (i.e. there are no separate pain pathways for cancer pain, and the receptors and structures involved in pain processing are identical) has been noted in numerous articles (*Peppin and Schatman. J Pain Res 2016*). Given the improved prognoses for cancer in general, there is also a significant overlap in the expected life expectancies between individuals with cancer pain and older patients with non-cancer pain. If the FDA had intended to limit the use of Duragesic, Nucynta, or Nucynta ER to cancer patients, they would have explicitly noted it in the label, as they have done for other medications.

On page 549 of his deposition and elsewhere, Dr. Kessler singles out 'back pain' and 'osteoarthritis' as 2 conditions in which Janssen inappropriately marketed opioids. I disagree with Dr. Kessler.

The use of Duragesic, Nucynta, and Nucynta ER and other opioids for back pain and osteoarthritis is based on clinical trials, and evidence-based guidelines developed by experts who have developed these guidelines. The American College of Rheumatology guidelines for hip and knee osteoarthritis in 2000 recommended tramadol, with stronger opioids indicated for patients who fail to respond to or cannot tolerate tramadol (*Altman et al. Arthritis Rheum 2000*). In their 2012 update, the use of opioids was conditionally recommended in patients with "an inadequate response to initial therapy (*Hochberg et al. Arthritis Care Res (Hoboken) 2012*). The Osteoarthritis Research Society International provided 2008 recommendations on the use of opioids for refractory hip and knee OA, with strong opioids reserved for the management of severe pain in certain circumstances (*Zhang et al. Osteoarthritis Cartilage 2008*). The Royal Australian College of General Practitioners Working Group guidelines for knee and hip osteoarthritis published in 2009 recommended opioids for severe osteoarthritis when joint replacement surgery was not indicated or delayed (*Guideline for the non-surgical management of hip and knee osteoarthritis. Melbourne: The Royal Australian College of General Practitioners, 2009*). In 2014, the United Kingdom's National Institute for Health and Care Excellence (NICE) recommends strong opioids for knee OA, especially in the elderly (*The National Clinical Guideline Centre (UK). Osteoarthritis: Care and management in adults. London: National Institute for Health and Care Excellence (UK); 2014 Feb.*).

For low back pain, several clinical practice guidelines have also evaluated opioid use. Joint guidelines by the American College of Physicians and American Pain Society found fair evidence for the use of opioids, with 2 of the 9 trials evaluated following patients for longer than 12 weeks (*Chou et al. Ann Intern Med 2007*). The 2008 American College of Environmental & Occupational Medicine guidelines (updated in 2011) did not recommend the 'routine use of opioids' for chronic non-malignant pain, but did recommend opioids for chronic pain in specific populations whose pain is not well-controlled (i.e. manifested by diminished function) by other approaches (*ACOEM's Guidelines for the Chronic Use of Opioids. Available at: https://www.nhms.org/sites/default/files/Pdfs/ACOEM%202011-Chronic%20Pain%20Opioid%20.pdf*). 2009 guidelines for the evidence-informed primary care management of low back pain, developed by 'Toward Optimized Practice Institute of Health Economics Date' (revised in November 2011) stated, "Long-term use of weak opioids, like codeine, should only follow an unsuccessful trial of non-opioid analgesics. In severe chronic pain, opioids are worth careful consideration. Long-acting opioids can establish a steady state blood and tissue level that may minimize the patient's experience of increased pain from medication withdrawal experienced with short acting opioids." (Available at: https://www.guidelinecentral.com/summaries/guideline-for-the-evidence-informed-primary-care-management-of-low-back-pain/). These guidelines have been widely disseminated by provincial governments in Canada such as Alberta and Edmonton. In addition to the above-mentioned North American guidelines, European guidelines have also recommended opioids in some

contexts (*Pongratz and Spath. MMW Fortschr Med 2001; Worz et al. MMW Fortschr Med 2001*).

D. DR. THOMAS GILSON

It is my understanding that Dr. Gilson testified as a representative of Cuyahoga County, during which he stated that the County, in responding to certain defendants' requests, identified certain medical claims involving prescriptions for opioid medications. Two of the criteria used were that the prescriptions were for non-cancer patients and that they were "high dose, that is 120 medical morphine equivalents or higher, which are far more dangerous." I disagree with the description of 120 morphine milligram equivalents (MME) as necessarily "high dose" or "far more dangerous" than other opioid prescriptions. First, the appropriate dose for a patient is highly variable and depends on a number of factors. Second, a 120 MME threshold is arbitrary, especially as to Duragesic. The FDA has approved Duragesic in 25, 50, 75, and 100 mcg/hour doses, yet under the County's criteria all prescriptions for Duragesic except for the 25 mcg/hour patch are "high dose" and "far more dangerous." As made clear by the CMS 2018 MME conversion table and notes (available at: https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Oral-MME-CFs-vFeb-2018.pdf), a 50 mcg/hour patch is 120 MME (50 mcg/hr fentanyl patch X (10 patches/30 days) X 7.2 = 120 MME/day). Third, Dr. Gilson appears to be basing the 120 MME threshold for Duragesic on a conversion table that assumes 100% bioavailability, but this assertion does not account for the well-documented fact that Duragesic is not 100% bioavailable because of various absorption and other issues (*Marguardt et al. Ann Pharmacother 1995; Solassol et al. Oncol Rep 2005*). Fourth, this threshold is also problematic for Nucynta and Nucynta ER, the active ingredient of which is tapentadol. Endnote ix to the 2018 MME conversion table notes, "Tapentadol is a mu receptor agonist and norepinephrine reuptake inhibitor. Oral MMEs are based on degree of mu receptor agonist activity, but it is unknown if this drug is associated with overdose in the same dose-dependent manner as observed with medications that are solely mu receptor agonists."

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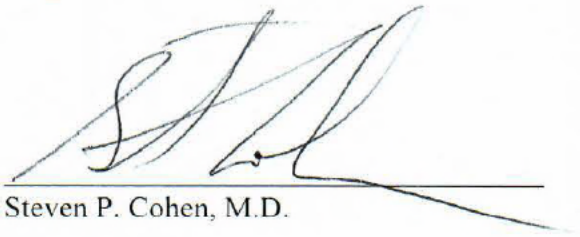
Dated: May 10, 2019



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